Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2001-03

Thiamethoxam

Helix, Helix XTra

The active ingredient thiamethoxam and associated end-use products Helix and Helix XTra (containing the insecticide thiamethoxam and the fungicides difenoconazole, metalaxyl-M and fludioxonil) for the control of flea beetles and seedling diseases on canola and mustard have been granted temporary registration under Section 17 of the Pest Control Products Regulations.

This regulatory note provides a summary of data reviewed and the rationale for the regulatory decision for these products.

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Publications Coordinator
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6602A
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.hc-sc.gc.ca/pmra-arla/
Information Service:
1-800-267-6315 or (613) 736-3799
Facsimile: (613) 736-3798

Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration for Thiamethoxam Technical, an insecticide developed by Syngenta Crop Protection Canada, Inc., and the associated end-use products Helix, and Helix XTra containing thiamethoxam and the currently registered fungicides difenoconazole, metalaxyl-M and fludioxonil, for use as a seed treatment on canola and mustard for the control of flea beetles and seedling diseases. These products are lindane and organophosphate replacement products and as such have been a work sharing project between the PMRA and the United States Environmental Protection Agency (EPA).

Methods for analysing thiamethoxam in environmental media are available to research and monitoring agencies upon request to the PMRA.

Syngenta Crop Protection Canada Inc. will be carrying out additional toxicology and value studies as well as a stewardship program as a condition of this temporary registration. Following the review of this information, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

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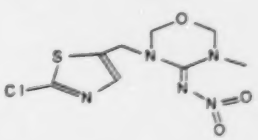
1.0 The active substance, its properties and uses

1.1 Identity of the active substance and impurities

Active substance:	Thiamethoxam
Function:	Insecticide
Chemical name:	
International Union of Pure and Applied Chemistry:	3-(2-chloro-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidene-*N*-nitroamine
Chemical Abstracts Service (CAS):	4*H*-1,3,5-oxadiazin-4-imine, 3-[(2-chloro-5-thiazoly)methyl]tetrahydro-5-methyl-*N*-nitro-
CAS number:	153719-23-4
Molecular formula:	$C_8H_{10}ClN_5O_3S$
Molecular weight:	291.7
Structural formula:	
Nominal purity of active:	98% nominal
Identity of relevant impurities of toxicological, environmental or other significance:	Nitrosamines are not detected at the limit of detection (LOD) of 0.5 ppm using a liquid chromatographic (LC) – transversely excited atmospheric method. Based on the raw materials, the manufacturing process used and the chemical structures of the active and impurities, the technical substance is not known to contain any toxic microcontaminants identified in Section 2.13.4 of Regulatory Directive DIR98-04, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*, or any Toxic Substances Management Policy (TSMP) Track-1 substances as identified in Appendix II of Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy.*

1.2 Physical and chemical properties of active substances and end-use product(s)

Table 1 Technical product: Thiamethoxam (CGA 293343)

Property	Result	Comment
Colour and physical state	Slightly cream crystalline powder	
Odour	Odourless	
Melting point or range	139.1 °C	
Boiling point or range	Not applicable	
Density	1.57×10^3 kg/m^3	
Vapour pressure	2.7×10^{-9} Pa at 20 °C 6.6×10^{-9} Pa at 25	Relatively nonvolatile
Henry's Law Constant at 20 °C	1.9×10^{-10} Pa m^3/mol	Nonvolatile from water and moist soil
Ultraviolet (UV) – visible spectrum	No significant absorption at wavelength over 300 nm in neutral, acidic and basic solutions	Not likely to phototransform in the environment
Solubility in water at 20 °C	4.1 g/L at 25 °C	Very soluble
Solubility (g/L) in organic solvents	Solvent — Solubility (g/L) acetone — 48 dichloromethane — 110 ethyl acetate — 7.0 hexane — <1 mg/L methanol — 13 octanol — 620 mg/L toluene — 680 mg/L	
n-Octanol–water partition coefficient (log K_{ow})	–0.13 ± 0.0017 at 25 °C	Low potential for bioaccumulation
Dissociation constant (pK_a)	No dissociation within the pH range 2–12	Not expected to dissociate
Stability (temperature, metals)	No thermal effect found between room temperature and the melting point of the substance No change by contact with metals (stainless steel, cast steel, tin and aluminum) and with metal ions (Zn^{+2}, Al^{+3}, Cu^{+2} and Fe^{+2})	

Table 2 End-use products: Helix XTra and Helix

Property	Result
Colour	Blue
Odour	Paint odour
Physical state	Liquid
Formulation type	Flowable
Guarantee	Active ingredient — Helix XTra — Helix Thiamethoxam — 20.7% — 10.3% Difenoconazole — 1.25% — 1.24% Fludioxonil — 0.13% — 0.13% Metalaxyl-M — 0.39% — 0.39%
Container material and description	Product — Container material Helix XTra — Metal and plastic 105 L, 200 L, 450 L, 1050 L and bulk Helix — Metal and plastic 105 L, 200 L, 450 L, 1050 L and bulk
Bulk density	Product — Density (g/mL) at 20°C Helix XTra — 1.29 Helix — 1.24
pH of 1% dispersion in water	Product — pH of 1% dispersion at 25°C Helix XTra — 6.6 Helix — 7–9
Oxidizing or reducing action	Products do not contain oxidizing or reducing agents
Storage stability	Both products have been shown to be stable at room temperature for 26 weeks
Explodability	Both products have no explosive potential

1.3 Details of uses

Helix and Helix XTra are liquid seed treatments that are proposed for use on canola and mustard for the control of flea beetles, seed-borne blackleg, and the seedling disease complex (damping-off, seedling blight, seed rot and root rot) caused by *Pythium* spp., *Fusarium* spp. and *Rhizoctonia* spp. Both formulations are composed of one insecticide (thiamethoxam) and three fungicides (fludioxonil, difenoconazole, metalaxyl-M). The proposed rate of application for each product is 1.5 L formulated product/100 kg seed. In terms of active ingredient, the proposed rates are as follows.

Active ingredient	Application rate (g a.i./100 kg seed)	
	Helix XTra	Helix
thiamethoxam	400.0	200.0
fludioxonil	2.5	2.5
difenoconazole	24.0	24.0
metalaxyl-M	7.5	7.5
Total	434.0	234.0

The difference between these products is the proposed rate of application for thiamethoxam and the proposed claim for the control of flea beetles. The proposed label for Helix (200 g thiamethoxam/100 kg seed) claims 14–21 days control of flea beetles after seedling emergence. The proposed label for Helix XTra (400 g thiamethoxam/ 100 kg seed) claims 28–35 days control of flea beetles after seedling emergence.

2.0 Methods of analysis (see Appendix I)

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

A detailed review of the toxicological database for the new insecticide, thiamethoxam (CGA 293343) was conducted. The database is complete, consisting of the full array of toxicity studies currently required for regulatory purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical; however, clarification of certain findings may be required as outlined below.

The toxicokinetics and metabolism of CGA 293343 was evaluated in rats and mice. In rats, approximately 84–95% was excreted in the urine and 2.5–6% was excreted in the faeces within 24 h. The parent compound accounted for the majority of the excreted radioactivity, while only two other metabolites accounted for up to 2% or more of the administered dose. Similar routes of transformation were apparent in rats and mice.

In acute toxicity studies, technical thiamethoxam was slightly toxic to rats and moderately toxic to mice via the oral route, of low toxicity to rats via the dermal and inhalation routes of exposure, minimally irritating to rabbit eyes and nonirritating to rabbit skin. Technical thiamethoxam was nonsensitizing in a dermal sensitization study in guinea pigs. The formulated product, Helix (10.3% thiamethoxam, 1.24% difenoconazole, 0.39% metalaxyl-M and 0.13% fludioxynil), was of low toxicity to rats via the oral, dermal and inhalation routes of exposure. Helix was minimally irritating to rabbit eyes, nonirritating to rabbit skin and nonsensitizing when tested in a dermal sensitization study in guinea pigs. Helix XTra (20.7% thiamethoxam, 1.25% difenoconazole, 0.39% metalaxyl-M and 0.13% fludioxynil) was of low toxicity to rats via the oral, dermal and inhalation routes of exposure. Helix XTra was minimally irritating to rabbit eyes, slightly irritating to rabbit skin and nonsensitizing when tested in a dermal sensitization study in guinea pigs.

In short-term toxicity studies in rats, the primary target organs were identified as kidney and liver. Males were more sensitive to effects on the kidneys than females. Liver toxicity was observed at higher doses, manifest as hepatocellular hypertrophy, increased liver weights and associated changes in clinical biochemical parameters (including increased cholesterol levels and activity of certain liver enzymes). It was postulated that the observed hyaline change in the proximal convoluted tubules of the male rat kidneys was due to the accumulation of α-2-μ globulin, a protein that is unique to male rats. While the observed kidney pathology is consistent with α-2-μ globulin mediated effects, no data were provided to confirm that α-2-μ globulin is present in the lesions or that it is the causative agent leading to the development of the observed kidney lesions. It should also be noted that the same hyaline change, consisting of eosinophilic droplets within the cytoplasm of the proximal convoluted tubules, was observed in one female of the F_1 generation in the two-generation rat reproduction study. In addition, other kidney toxicity was observed in female rats, consisting of chronic tubular lesions and nephrocalcinosis. Data should be generated confirming that thiamethoxam or metabolite(s) of thiamethoxam bind to α-2-μ globulin, and that this complex is present in the observed lesions; otherwise, the kidney findings must be considered relevant in characterizing the hazard profile of thiamethoxam.

The 28-day dermal toxicity study revealed systemic effects that were consistent with those observed in dietary studies; however, females were more sensitive than males. The hyaline change in renal tubules was observed only in high-dose males, and liver and kidney toxicity were observed in mid-dose females.

There was no evidence of oncogenicity after chronic administration of thiamethoxam in rats. Systemic toxicity was observed in males and females, manifest as chronic nephropathy and lymphocytic infiltration in the kidneys of males and decreased body weight gain, chronic tubular lesions in the kidneys and foci of cellular alteration in the liver of females. Body weight was unaffected in males, leading to questions on the adequacy of the high dose. The dose selection, however, was based on the observed reduction in body weight gain (approximately 20% at 1250 ppm) in the subchronic toxicity study. On the basis of the available data, it appears that higher doses could have been tolerated by the animals, leading to uncertainty regarding the toxic effects

(particularly liver pathology) that would be observed in rats upon chronic exposure to higher doses of thiamethoxam.

In mice, the primary target organ was the liver, and males were more sensitive to the liver pathology than females. In subchronic and chronic studies, liver pathology included hepatocellular hypertrophy, necrosis of single hepatocytes, lymphocytic infiltration and Kupffer cell pigmentation (subchronic) or Kupffer cell hyperplasia (chronic). Chronic dosing resulted in the development of benign and malignant liver tumours in both sexes. There was an increase in the number of animals with multiple tumours; however, treatment did not affect the latency to tumour formation or lethality from the observed tumours. The incidence of non-neoplastic and neoplastic pathology was increased at the same dose level, i.e., there was no clear departure point between doses that induced tumours and other systemic toxic effects. On the basis of the observed tumour response, it was concluded that thiamethoxam demonstrated oncogenic potential in mice. Subchronic administration of high doses resulted in decreased ovarian weights and ovarian atrophy. In the dog, the main target organ appeared to be the testis. In the 90-day study, the high dose initially caused severely decreased food consumption and concomitant body weight loss, necessitating cessation of treatment for seven days and resumption at a lower dose. Animals in this group had decreased testis weights, reduced spermatogenesis and minimal to moderate occurrence of spermatic giant cells in the testes. Atrophy of the seminiferous tubules was observed in one high-dose male. In addition, decreased ovary weights associated with delayed maturation of the ovaries was observed at this dose. Atrophy of the seminiferous tubules and decreased testis weight were observed after 12 months of treatment with thiamethoxam. In both the 90-day and the one-year study, significant decreases were observed in alanine aminotransferase (ALT) activity. While the significance of this observation is not fully understood, there is no doubt regarding its association to treatment with thiamethoxam. It has been proposed that the decreases in ALT may be caused either by interference with or suppression of in vivo concentrations of pyridoxal phosphate (vitamin B6, a cofactor necessary for ALT activity) or by direct suppression of ALT synthesis. If thiamethoxam interferes with vitamin B6, it could have significant implications regarding potential adverse developmental effects. Hematological parameters (primarily prolonged prothrombin times) were affected at higher doses.

Thiamethoxam was tested in a battery of five in vitro and in vivo genotoxicity studies. There was no evidence of genotoxicity in any of the studies.

There was no evidence of teratogenicity in developmental toxicity studies in rats and rabbits, and thiamethoxam did not affect the standard reproductive indices (mating, gestation, fertility, viability) in a two-generation reproductive toxicity study. Atrophy of the seminiferous tubules was observed in the F_1 generation in the absence of parental systemic toxicity, however, indicating the potential for increased qualitative and quantitative sensitivity of the young. The animals in which this observation occurred were the only animals that were exposed to thiamethoxam both in utero and postnatally. It was not observed in the F_0 generation, nor was it observed in any of the subchronic or chronic toxicity studies conducted in rats. Atrophy of the seminiferous tubules was, however, observed in adult dogs in both the 90-day and the one-year studies. The NOAEL for this observation (atrophy of the seminiferous tubules among F_1 males) is the

critical NOAEL from the entire toxicity database for thiamethoxam (0.6 mg/kg bw/d). Decreased testis weights were observed in high-dose F_1 males. In addition, systemic target organ toxicity was observed in male kidneys that was consistent with the findings in the short-term studies; however, the observation of the hyaline change in one high-dose F_1 female raises some uncertainty regarding the claim that this finding in male rats in numerous other studies is due to the accumulation of a protein specific to the male rat, α-2-μ globulin, in the proximal convoluted tubules.

Acute high doses of thiamethoxam resulted in effects on functional observational battery (FOB) and locomotor activity (LMA) parameters, most likely attributed to general toxicity. There was no neurotoxicity observed in a subchronic neurotoxicity study and there was no neurohistopathology after acute or subchronic dosing.

A number of parameters were affected in various species following treatment with thiamethoxam for varying durations that suggest possible interaction with endocrine systems. The specific findings in rats included increased plasma cholesterol, hepatocellular hypertrophy, increased adrenal weights, fatty change of the adrenal cortex and hypertrophy of thyroid follicular epithelium. In the two-generation reproductive toxicity study, decreased testis weights and increased incidence and severity of atrophy of seminiferous tubules were observed in the F_1 generation. Equivocal results in sperm motility were subsequently investigated in a separate, complementary study that was restricted to assessment of sperm parameters in F_0 animals; hence, no information is available regarding this observation in F_1 animals, where adverse effects were noted in the seminiferous tubules. In mice, high doses caused decreased ovary weight and ovarian atrophy in the 90-day study and a slight, transient increase in adrenal weight in females at interim sacrifice in the oncogenicity study. In dogs, decreased testis and ovary weight were observed in the 90-day study at a dose that resulted in significant body weight loss, necessitating cessation of treatment for seven days and resumption at a lower dose. These organ weight changes were accompanied by histopathological evidence of delayed maturation in the ovaries and reduced spermatogenesis with minimal to moderate occurrence of spermatic giant cells in the testes. Atrophy of the seminiferous tubules was the key observation in the establishment of the NOAEL in the one-year dog study (see Appendix II, Table 2).

A developmental neurotoxicity study is required for the following reasons:

- evidence of endocrine effects across species and dosing durations;
- neurotoxic mode of action of thiamethoxam in insects;
- possibility of interference with pyridoxal phosphate (based on decreased ALT activity in dog studies); and
- evidence of increased qualitative and quantitative susceptibility of the young in the rat reproduction study.

In consideration of the above rationale for requiring a developmental neurotoxicity study, an additional safety factor of 10× will be applied to the occupational and dietary risk assessments for thiamethoxam to protect susceptible subpopulations including fetuses of pregnant workers.

3.2 Determination of acceptable daily intake

The recommended acceptable daily intake (ADI) for thiamethoxam is 0.0006 mg/kg bw/d. The most appropriate study for the selection of a toxicity end point for chronic dietary exposure was the two-generation reproduction study in rats, which had a NOAEL of 0.6 mg/kg bw/d, based on increased incidence of tubular atrophy in the testes of the F_1 generation. The standard uncertainty factor of 100 is applied to account for intraspecies and interspecies variability. A developmental neurotoxicity study is required based on the insecticidal mode of action of thiamethoxam, the evidence of increased susceptibility of the young and in consideration of the endocrine effects observed throughout the toxicity database for thiamethoxam; therefore, an additional safety factor of 10 is applied.

3.3 Acute reference dose

Thiamethoxam was of low to moderate acute toxicity by the oral, dermal and inhalation routes of exposure. In the acute neurotoxicity study, the NOAEL was set at 100 mg/kg bw, based on increased incidence of FOB and LMA findings. The standard uncertainty factor of 100 is applied to account for intraspecies and interspecies variability. A developmental neurotoxicity study is required based on the insecticidal mode of action of thiamethoxam, the evidence of increased susceptibility of the young and in consideration of the endocrine effects observed throughout the toxicity database for thiamethoxam; therefore, an additional safety factor of 10 is applied. The acute reference dose (ARfD) for thiamethoxam is 0.1 mg/kg bw.

3.4 Toxicological end point selection: occupational and bystander risk assessment

Exposure to the commercial seed treatment workers would occur on approximately 90 days over the treating season. Dermal and inhalation exposure are the predominant routes of exposure.

For the noncancer risk assessment, based on the nature of the findings in the rat reproductive toxicity study, and in consideration of the endocrine activity observed throughout the database, it was considered appropriate to use the NOAEL of 0.6 mg/kg bw/d from that study in the occupational risk assessment. A developmental neurotoxicity study is required based on the insecticidal mode of action of thiamethoxam, the evidence of increased susceptibility of the young and in consideration of the endocrine effects observed throughout the toxicity database for thiamethoxam; therefore, an additional safety factor of 10 is applied and the target margin of exposure (MOE) is 1000.

It was considered appropriate to ensure that the occupational risk assessment also addressed workers who may have occasional elevated exposures. The relevant end point for these exposures is the NOAEL used in establishing the dietary acute reference dose (i.e., NOAEL of 100 mg/kg bw from the acute neurotoxicity study in rats). The target MOE for this end point is 1000.

For the cancer risk assessment, in view of the uncertainty regarding the mode of action leading to the observed tumour response, it was considered appropriate to use a quantitative approach to the cancer risk assessment. Unit risks for thiamethoxam, denoted by Q_1^* (representing the upper 95% confidence limit on the slope of the dose–response curve in the low-dose region) were calculated based on the bioassay data from the mouse oncogenicity study. The unit risk of 3.77×10^{-2} $(mg/kg\ bw/d)^{-1}$ was used for the cancer risk assessment for commercial seed (canola, mustard) treatment workers handling Helix and Helix XTra.

3.5 Impact on human and animal health arising from exposure to the active substance or to its impurities

3.5.1 Operator exposure assessment

The proposed end-use product, Helix, has a guarantee of 10.3% thiamethoxam and proposed application rate of 1.5 L product/100 kg canola or mustard seed (i.e., 200 g a.i./100 kg seed). The proposed end-use product, Helix XTra, has a guarantee of 20.7% thiamethoxam and proposed application rate of 1.5 L product/100 kg canola or mustard seed (i.e., 400 g a.i./100 kg canola or mustard seed).

Dermal absorption

Potential dermal absorption of thiamethoxam was investigated in an in vivo rat study. The test material was applied as Helix 289 FS at two dose levels, a low dose (3.64 $\mu g/cm^2$) and a high dose (36.4 $\mu g/cm^2$). Following a 10-h exposure, the application site was washed and subgroups of four animals were sacrificed at various times postdosing. As a goal of the study was to characterize the fate of skin site residues, groups of animals were sacrificed at 10, 24, 72, 168 and 336 h postdosing. Urine and faeces were collected daily.

Following dermal administration, the majority of the administered dose was recovered from the skin wash. The percent of applied dose accounted for by skin washes and rinse of the dose site appliance ranged from 63.16 to 75.7%. Significant quantities were also present at the application site after washing (i.e., 18.3–28.38%). Skin site residues did not decline significantly over the 336-h postdosing period. The majority of the absorbed dose was present in the urine (0.60–3.36%), with smaller quantities present in the faeces (0.01–0.36%), blood (0.0032–0.032%), cage wash (0.02–0.2%) and carcass (0.042–0.47%).

For the Helix low dose group (3.64 $\mu g/cm^2$), percent dermal absorption (excluding residues retained at the skin site) increased with increasing time postdosing. After 10 h, dermal absorption was 1.27%. This value increased to 1.42% at 24 h, 1.48% at 72 h, 1.91% at 168 h and 4.22% at 336 h postdosing.

For the Helix high dose group (36.4 $\mu g/cm^2$), there was a general trend of increasing percent dermal absorption (excluding residues retained at the skin site) with increasing time postdosing. After 10 h, dermal absorption was 1.21%. This value was 1.03% at 24 h, 1.24% at 72 h, 2.47% at 168 h and 2.14% at 336 h postdosing.

Analysis of cumulative radioactivity in the urine over time suggests that thiamethoxam may continue to diffuse slowly through the skin into systemic circulation throughout the 336-h postdosing period. Although continued absorption of skin site residues may occur beyond 336 h, this is expected to be limited due to the demonstrated slow loss of residues from the skin site and the extent of epidermal exfoliation that typically occurs over a two- to three-week period in mammals. As such, use of a dermal absorption value of 5% in cancer and noncancer occupational risk assessments is considered to adequately account for the small amount of continued absorption from the skin site.

A study limitation was that numerous rats appeared to access the dose site, particularly in the latter part of the study, and this made interpretation of the results for these animals difficult. These animals (11 of 68) were therefore not included in calculations of percent dermal absorption.

Occupational exposure study

An occupational exposure study was conducted to quantify exposure to thiamethoxam when formulated as a liquid for commercial seed treatment. The study was comprised of these three phases, (*i*) method development phase, (*ii*) pilot phase in the field and (*iii*) full field phase. Passive dosimetry methodology was used.

The study monitored 93 full-day replicates across five representative commercial seed treatment sites and captured the following work functions and personal protective clothing scenarios:

- treaters wearing chemical-resistant coveralls over long-sleeved shirt and long pants and gloves;
- cleaners wearing chemical-resistant coveralls over long-sleeved shirt and long pants and gloves;
- baggers/sewers/stackers wearing chemical-resistant coveralls over long-sleeved shirt and long pants and gloves;
- baggers/sewers/stackers wearing regular coveralls over long-sleeved shirt and long pants and gloves; and
- forklift operators wearing regular coveralls over long-sleeved shirt and long pants and gloves.

Average daily exposure estimates were derived for commercial seed treatment workers handling Helix or Helix XTra. Estimates were based on arithmetic mean unit exposure values, the proposed application rates, average facility through-put of 40 000 kg seed/day, a dermal absorption value of 5% and a body weight of 70 kg. A respiratory protection factor of 90% was applied for half-mask respirators or fresh air hoods and 50% for other respiratory protection, such as dust masks. Lifetime average daily exposures were also calculated based on a use pattern of 90 days/year, over a working tenure of 40 years, over a 75-year lifespan.

For treaters (including routine maintenance and clean-up) handling Helix wearing chemical-resistant coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, and half-mask respiratory protection, daily systemic exposure (dermal + inhalation) would be 0.45 μg/kg bw/d. For treaters handling Helix XTra, daily systemic exposure was estimated to be 0.90 μg/kg bw/d. The lifetime average daily dose for treaters handling Helix was estimated to be 0.059 μg/kg bw/d. For treaters handling Helix XTra, the lifetime average daily dose was estimated to be 0.12 μg/kg bw/d.

At some facilities, workers conduct occasional full or partial day clean-ups prior to changing seed varieties. These exposures were within the range of exposures of the treater exposures, with the higher exposures for those clean-up functions attributed to poor industrial hygiene procedures (e.g., use of compressed air to clean enclosed spaces such as treating equipment). An upper bound exposure for all workers is represented by the maximum individual exposure, which occurred for a treater who conducted significant cleaning activities during the monitoring period (i.e., 4.21 μg/kg bw/d for Helix and 8.42 μg/kg bw/d for Helix XTra).

For baggers/sewers/stackers handling Helix treated seed, wearing regular coveralls over long-sleeved shirt and long pants, chemical-resistant gloves and dust masks, daily systemic exposure (dermal + inhalation) was estimated to be 0.217 μg/kg bw/d. For baggers/sewers/stackers handling Helix XTra treated seed, daily systemic exposure was estimated to be 0.434 μg/kg bw/d. The lifetime average daily dose for baggers/sewers/stackers handling Helix treated seed was estimated to be 0.0285 μg/kg bw/d. For baggers/sewers/stackers handling Helix XTra treated seed, the lifetime average daily dose was estimated to be 0.058 μg/kg bw/d.

For forklift operators in facilities using Helix, wearing regular coveralls over long-sleeved shirt and long pants, and gloves, daily systemic exposure (dermal + inhalation) was estimated to be 0.16 μg/kg bw/d. At facilities using Helix XTra, daily systemic exposure was estimated to be 0.32 μg/kg bw/d. The lifetime average daily dose for forklift operators at facilities using Helix was estimated to be 0.021 μg/kg bw/d. At facilities using Helix XTra, the lifetime average daily dose was estimated to be 0.042 μg/kg bw/d.

Margins of exposure for noncancer end points based on the NOAEL of 0.6 mg/kg bw/d in the rat reproductive toxicity study are outlined below.

Worker subpopulation	Helix		Helix XTra	
	Daily exposure (μg/kg bw/d)	MOE	Daily exposure (μg/kg bw/d)	MOE
Treater	0.45	1340	0.9	670
Bagger/Sewer/Stacker	0.217	2760	0.434	1380
Forklift operator	0.16	3750	0.32	1875

Margins of exposure were also derived for workers who may have occasional elevated exposures. The relevant end point for these acute exposures is the NOAEL used in establishing the dietary acute reference dose (i.e., NOAEL of 100 mg/kg bw from the acute neurotoxicity study in rats). Based on the upper bound exposure estimate of 4.21 μg/kg bw/d for workers handling Helix and 8.42 μg/kg bw/d for workers handling Helix XTra, this yields MOEs of 24 000 and 48 000 for Helix and Helix XTra, respectively.

For the noncancer risk assessment, all MOEs for workers handling Helix are acceptable. For Helix XTra, MOEs are acceptable for the risk assessments for acute exposures for all workers, and for repeated exposures for the bagger/sewer/stacker and forklift operator. For Helix XTra, lower MOEs for treaters (i.e., 670) were attributed to certain work practices that resulted in elevated exposures (e.g., use of compressed air to clean the interior of treating equipment). The applicant has committed to implementation of a product stewardship program designed to mitigate exposure to Helix XTra. The product stewardship program is comprised of the following elements: training, glove provision, label restrictions regarding the use of compressed air for cleaning, on-site stewardship, and appropriate feedback mechanisms. Implementation of this product stewardship program will decrease exposures, and MOEs for treaters handling Helix XTra will increase to an acceptable level.

For the cancer risk assessment, lifetime average daily exposure estimates and the unit risk of 3.77×10^{-2} (mg/kg bw/d)$^{-1}$ were multiplied to yield the following lifetime risk levels.

Worker subpopulation	Helix		Helix XTra	
	Lifetime average daily exposure (μg/kg bw/d)	Risk level	Lifetime average daily exposure (μg/kg bw/d)	Risk level
Treater	0.059	2×10^{-6}	0.12	4.5×10^{-6}
Bagger/Sewer/Stacker	0.0285	1×10^{-6}	0.058	2×10^{-6}
Forklift operator	0.021	0.8×10^{-6}	0.042	1.6×10^{-6}

For Helix XTra, the calculated risk levels will be reduced by the implementation of the product stewardship program. These risk levels are considered acceptable.

3.5.2 Bystanders

N/A

3.5.3 Workers

Quantitative exposure estimates were not derived for farmers planting treated canola and mustard seed. Given that the volume of seed handled is substantially lower than during commercial seed treatment, that contact with the seed would be limited, that chemical-resistant gloves must be worn when handling treated seed and that exposure would be short-term, the potential for postapplication exposure should be lower than that estimated for commercial seed treaters.

4.0 Residues

4.1 Residue summary

The metabolism of thiamethoxam in pears, cucumbers, corn and rotational crops is similar, although the relative levels of individual metabolites differed among the three primary crops. Due to the quantitative differences observed in the cucumber metabolism study, we cannot conclude that the metabolism of thiamethoxam in plants is understood. The corn metabolism study is considered to be the most relevant to the petitioned use of a seed treatment on canola. To varying degrees, the metabolism of thiamethoxam in each of these crops involves: (*i*) opening of the oxadiazine ring by hydrolysis, (*ii*) loss of the nitro group, (*iii*) hydrolysis of the guanidine moiety to urea derivatives, (*iv*) cleavage of the N–C bridge between the two ring systems and (*v*) *N*-demethylation of the oxadiazine ring or its derivatives. Although the extract sequence of these reactions in individual crops is uncertain, metabolites resulting from each of these reactions were present in pears, cucumbers and corn.

The metabolism of thiamethoxam in rat, ruminants and poultry is similar. The major pathway of metabolism involves hydrolysis of the oxadiazine ring to form CGA 322704 and subsequent demethylation to produce CGA 265307; loss of the nitro group from these two metabolites also yields NOA 421275 and NOA 421276. Several major metabolites (MU3, L14 and MU12) in both ruminants and poultry also result from the reduction of the nitro group in thiamethoxam or CGA 265307 to a hydrazine, and subsequent conjugation with acetic or 2-oxo-propionic acids. Separation of the thiazole and oxadiazine rings was only a minor pathway in ruminants and poultry.

The environmental fate of thiamethoxam was also evaluated. Thiamethoxam is hydrolyzed rapidly under basic conditions to produce CGA 355190, NOA 404617 and CGA 309995. These transformation products were also observed in the metabolic profiles of the rat and therefore do not represent novel metabolites. Aerobic and anaerobic metabolism of thiamethoxam resulted in the formation of many metabolic intermediates, none of which were considered unique. It is therefore unlikely that the transformation products of thiamethoxam resulting from environmental hydrolysis and aerobic and anaerobic biotransformation in soil will lead to the accumulation of metabolites in food crops that were not identified in the plant and animal metabolism studies.

No information on photolysis was reviewed, as the proposed use is as a seed treatment.

Based on all of the metabolism studies, the ROC is defined as parent and metabolite CGA 322704, namely 3-[(2-chloro-5–thiazolyl)methyl]tetrahydro-5-methyl-*N*-nitro-4*H*-1,3,5-oxadiazin-4-imine and the metabolite 1-(2-chloro-triazol-5-ylmethyl)-3-methyl-*N*-nitro-guanidine.

Plant commodities. Syngenta HPLC–UV (or MS) Method AG-675 is adequate for collecting data on residues of thiamethoxam and CGA-322704 in and on canola. Adequate method validation data were submitted for canola seed and on various additional crop matrices. The method has been adequately radiovalidated, and it has undergone a successful ILV trial. The validated LOQ for residues of each analyte is 0.01 ppm in all plant matrices with the exception of fruit juices (0.005 ppm).

Animal commodities. Adequate method validation data using animal commodities have been submitted for Syngenta HPLC–MS Method AG-675, and the method has undergone a successful ILV trial using milk, eggs and beef liver. The validated LOQ for residues of thiamethoxam and CGA 322704 is 0.01 ppm each in meat, poultry and eggs, and 0.005 ppm each in milk. This method has also been adequately radiovalidated using samples of meat and milk from the goat metabolism study.

Multiresidue method. Poor recoveries for thiamethoxam and metabolite CGA 322704 were obtained using the multiresidue protocols. Therefore, for regulatory purposes, the residues of thiamethoxam and CGA 322704 will not be quantified using a multiresidue method.

The submitted two-year storage stability study on thiamethoxam per se and one-year interim study on CGA 322704 are adequate pending submission of a detailed description of Method REM 179.03, used to determine residues of each analyte in some study samples. The available data indicate that residues of CGA 322704 and thiamethoxam are stable stored at –18°C in apples, corn grain, potato, canola seed and tomato for up to one and two years, respectively. HED assumes that Method REM 179.03 is similar to Method REM 179.01 (described above); however, Method REM 179.03 is capable of determining residues of parent and CGA 322704.

Interim data from the ongoing storage stability study is adequate and indicate that residues of thiamethoxam and CGA 322704 are stable in and on canola oil, corn meal, leaf lettuce, safflower seed and tomato puree for up to four months at –20°C.

Samples of canola and mustard seed from the residue field trials were stored frozen for 2–11 months from collection to analysis. The storage intervals and conditions of the residue studies are adequately supported by the storage intervals depicted in the available storage stability studies.

Freezer storage stability of thiamethoxam and metabolite CGA 322704 in animal matrices was not addressed.

A total of 26 trials (18 trials in Canada) were conducted with either Helix or with thiamethoxam alone. Combined residues of thiamethoxam and CGA 322704 were below the combined LOQ (<0.02 ppm) in and on all (26 trial locations in all) samples of canola seed grown from seed treated with thiamethoxam at 500 g a.i./100 kg seed (0.5 lb a.i./100 lb seed; ~1× the maximum proposed use rate) and harvested at maturity, 87–295 days after planting. These data support the proposed maximum residue limit

(MRL) of 0.02 ppm for residues of thiamethoxam and CGA 322704 in and on canola seed.

The chromatograms submitted with these studies indicated that the areas of elution did not contain matrix interferences. These chromatograms also showed good consistency in peak shape, height and retention times.

The combined residues of thiamethoxam and CGA 322704 were below the combined LOQ (<0.1 ppm) in and on 10 mustard seed samples grown from seed treated with thiamethoxam at 400 g a.i./100 kg seed (0.4 lb a.i./100 lb seed) and harvested at maturity, 101–104 days after planting. An MRL of 0.02 ppm is therefore recommended to cover potential residues of thiamethoxam and metabolite CGA 322704 in mustard seed. In all cases, adequate chromatographic evidence was provided. The chromatographic evidence indicated consistent peak shape and retention times and also illustrated that there were no matrix interferences in the area of elution.

As treatment at ~3× the maximum proposed application rate did not result in quantifiable residues of thiamethoxam and CGA 322704 in canola seed samples, and as residues in and on canola seed from all field trials conducted at ~1× were less than the LOQ, no further processing data or MRLs for residues in processed commodities are required for canola. The maximum theoretical concentration factor for canola is 3×. The residues of thiamethoxam and CGA 322704 in the processed fractions will therefore be covered by the MRL on the raw agricultural commodity.

Using the proposed U.S. tolerances (from the petitioned use pattern), daily intake of thiamethoxam for beef cattle is 0.93 ppm, based on a diet consisting of 40% apple pomace, 20% cotton gin by-products, 25% wheat forage and 15% barley or wheat grain, and 1.43 ppm for dairy cattle based on a diet consisting of 60% wheat forage, 20% cotton gin by-products and 20% barley or wheat grain. The expected residues in canola meal is 0.0015 ppm. Based on a ~2.0 ppm feeding level, the PMRA can conclude that there are no finite residues transferred into the meat and milk.

The maximum theoretical dietary burden of thiamethoxam for swine and poultry is 0.025 ppm, based on a diet consisting of 85% sorghum grain and 15% cottonseed meal for swine, and 80% wheat or sorghum grain and 20% cottonseed meal for poultry. As the 2 ppm feeding level in the submitted study represents 80× the theoretical dietary burden for swine, there is no reasonable expectation of the transfer of thiamethoxam residues from feed items to hog commodities. In the poultry metabolism study, hens were dosed at ~100 ppm, equivalent to ~4000× the maximum dietary burden. Based on data from the metabolism study, residues of thiamethoxam and CGA 322704 in tissues and eggs would be expected to be less than 0.01 ppm even at a 100× feeding level.

As outlined above, there is little expectation that there will be a transfer of the residues (thiamethoxam and CGA 322704) into the meat, milk and eggs. Under these conditions, MRLs will be recommended but, based on the fact that there is no expectation of finite residues in animal commodities, they will not be used for dietary risk calculations.

We recommend MRLs of 0.02 (LOQ) be established to cover potential residues of thiamethoxam and CGA 322704 in meat, meat by-products and eggs. An MRL of 0.01 (LOQ) will be recommended to cover the potential residues of thiamethoxam and CGA 322704 in milk.

Using a Q* value in the Dietary Exposure Evaluation Model (DEEM), field trial data for canola and no contribution for drinking water, the lifetime cancer risk from a dietary exposure was estimated to be in the range of 5.0×10^{-9} to 2.75×10^{-10}. This is considered adequate. The exposure assessment did not include a dietary contribution from meat, milk and eggs, since the information available to us demonstrated that from this use pattern, no finite residues would be expected in these commodities. The seed treatment use of thiamethoxam does not pose an unacceptable health risk.

5.0 Fate and behaviour in the environment

Thiamethoxam was determined to be very soluble in water. The vapour pressure of thiamethoxam indicated that the compound would be considered relatively nonvolatile under field conditions. The Henry's Law Constant indicated that the chemical will be nonvolatile from water and moist soil. The magnitude of the *n*-octanol–water partition coefficient for thiamethoxam indicated a low potential for bioaccumulation. The compound is not expected to dissociate. The UV–visible absorption spectrum of thiamethoxam indicated that the compound was not likely to phototransform at environmentally relevant wavelengths of light.

Hydrolysis will not be a route for transformation or dissipation of thiamethoxam in acidic to neutral environmental media, but will be important in an alkaline environment. Based on results of the laboratory studies of biotransformation, thiamethoxam is classed as moderately persistent to persistent and the biotransformation product CGA 353968 is classed as persistent in aerobic soil.

The adsorption K_{oc} of ^{14}C-guanidine thiamethoxam in six agricultural soils indicated that thiamethoxam has a medium to very high potential for mobility in the soil. There was no correlation apparent in the data between the adsorption K_d value and percent organic carbon or percent clay content of the soils. The desorption K_{oc} of ^{14}C-guanidine thiamethoxam indicated that once adsorbed to soil, thiamethoxam would be less likely to be mobile in the soil. Results of an aged soil column leaching study indicated that thiamethoxam will be less mobile in soil after ageing. The mobility of the major transformation product CGA 355190 or that of its subsequent transformation product CGA 353968, however, were not investigated.

Canadian field dissipation studies conducted at four sites with Helix seed treatment (i.e., with treated seed) indicated that thiamethoxam is moderately persistent in soil under field conditions. Residues of the major transformation products CGA 355190 and CGA 322704 were detected at all four sites. The persistence of these major transformation products, however, was not characterized but is expected to be greater than that of the parent compound. Residues of thiamethoxam remained in the top 10 cm

of soil, with occasional detection near the LOD in the 10–25 cm depth of soil, indicating that the product did not leach appreciably under conditions of the seed treatment field study.

6.0 Effects on nontarget species

The environmental toxicology data package for the seed treatment use encompasses a limited data set, owing to the limited exposure of most nontarget organisms, except wild birds, to the chemical. Therefore, only avian toxicity data were reviewed.

The results indicated that thiamethoxam technical was slightly toxic to two avian indicator species: the bobwhite quail and the mallard duck. The subacute dietary toxicity studies in the bobwhite quail and the mallard duck with thiamethoxam indicated that the compound was practically nontoxic to both species. In one-generation reproduction studies with the bobwhite quail and the mallard duck, thiamethoxam did not cause significant treatment-related effects on mortality or reproductive parameters. There were, however, internal abnormalities revealed in some individuals during post-mortem examinations.

A risk assessment, based on dietary exposure, indicated that thiamethoxam will not pose an appreciable risk to wild birds.

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended use

Helix and Helix XTra seed treatments are proposed for use on canola and mustard for the control of flea beetles, seed-borne blackleg, and the seedling disease complex (damping-off, seedling blight, seed rot and root rot) caused by *Pythium* spp., *Fusarium* spp. and *Rhizoctonia* spp. The difference between these products is the proposed rate of application for thiamethoxam and the proposed claim for the control of flea beetles. The proposed label for Helix (200 g thiamethoxam/100 kg seed) claims 14–21 days control of flea beetles after seedling emergence. The proposed label for Helix XTra (400 g thiamethoxam/100 kg seed) claims 28–35 days control of flea beetles after seedling emergence.

7.1.2 Mode of action

Thiamethoxam is a broad spectrum insecticide that belongs to a new class of compounds, the neonicotinoids. While laboratory data indicates that thiamethoxam interferes with the nicotinic acetylcholine receptors of the insect's nervous system, the specific binding site(s) or receptor(s) is unknown at this time. Although imidacloprid, also a neonictinoid insecticide, is also known to interfere with nicotinic acetyl choline receptors, thiamethoxam appears to function at a different location. Thiamethoxam does not inhibit

cholinesterase or interfere with sodium channels and, therefore, has a different mode of action than organophosphate, carbamate and pyrethroid insecticides. Thiamethoxam is reported to act through contact and ingestion, and display translaminar and systemic activity. It is reported to have excellent acropetal translocation in the xylem and no basipetal movement in the phloem.

Difenoconazole is a locally systemic fungicide in the sterol inhibitor class. Metalaxyl-M is a systemic acylamide that inhibits RNA synthesis in Oomycetes. Fludioxonil is a nonsystemic classed as a phenylpyrrole and acts on cell membranes. Preliminary field trials with these individual fungicide actives did not produce expected results on canola, as soil pathogens other than those controlled by each tested active reduced plant stand. As a result, the Helix formulation contains a combination of three complementary fungicides to cover the range of soilborne pathogens that also provide some overlap in activity. Disease control is proposed for seeds and seedlings up to the four-leaf stage.

7.1.3 Effectiveness against pest

7.1.3.1 Description of pest problem

Flea beetles

Flea beetles (*Phyllotreta* spp.) are considered to be a chronic, but erratic, pest problem wherever canola is grown in North America. In Canada, flea beetle populations have historically been highest in eastern Saskatchewan and Manitoba. Damage is caused by overwintering adult beetles that migrate into canola fields in the spring. Adults feed on the epidermis of the cotyledons and first true leaves of canola seedlings, causing pitting. Damaged plants typically have a "shot-holed" appearance when the tissues around the feeding sites in the cotyledons and leaves die. Generally, under good growing conditions, canola seedlings can withstand removal of up to 50% of the leaf area in the cotyledon stage without a significant reduction in yield. With heavy attacks, seedlings may wilt and die, particularly when feeding is combined with poor plant growth, such as during hot, dry weather. Less severe beetle damage may cause stunting and uneven maturity in growth stages. The heaviest feeding can last from May to late June when the crop is most susceptible. If the crop has good growing conditions and adequate soil moisture, it can often outgrow a moderate flea beetle attack and damage with no loss in yield. Once the crop develops beyond the seedling stage, damage does not usually occur and the adult flea beetle population often begins to decline. The first 21 days after seedling emergence is generally considered to be the most critical period for protection against flea beetle attack to avoid crop losses.

Diseases

The diseases for which Helix is targeted originate from fungal pathogens in soil or crop debris in most regions where canola and mustard are grown. Blackleg symptoms, caused by *Leptosphaeria maculans*, may appear on leaves, stems and pods of cruciferous plants. Initial inoculum is formed on infested crop debris on or in soil, and spores are spread by air to adjacent seedlings where lesions develop. Less commonly, symptoms develop from seed that has been infected prior to harvest. Early infections can result in stem cankers, seedling death and reduced plant stand. Yield is reduced due to loss of plants, shrivelled

seed and pod shattering. Mustard is not usually affected by blackleg but may act as a host crop.

Pythium, *Fusarium* and *Rhizoctonia* species cause seed rot and damping-off of seedlings in a wide range of crops in areas where soils are cool and wet during germination and emergence, such as the northwest Prairies or in low areas of drier fields. Disease is not easy to quantify but typically results in reduced seedling stands at or shortly after emergence. Plants that survive may have damaged root systems, resulting in lower vigour and yield.

7.1.3.2 Laboratory trials

Flea beetles

Results were submitted from two growth chamber trials that assessed the efficacy of thiamethoxam seed treatment (Helix XTra) against flea beetles under controlled laboratory conditions. In one trial, the residual efficacy of thiamethoxam and lindane seed treatments was compared by conducting leaf damage assessments on artificially infested canola seedlings at 5–42 days after germination. Statistically, there was no significant difference in the performance of thiamethoxam applied at rates of 200 and 400 g a.i./100 kg seed. Both lindane and thiamethoxam provided equivalent control up to 10 days following seedling emergence, with significantly lower flea beetle damage compared with the untreated check. At 12 days following emergence, damage to plants treated with lindane was significantly higher than for thiamethoxam, but was still significantly lower than the untreated control. At 15–19 days following emergence, flea beetle damage on the thiamethoxam-treated seedlings was significantly lower than on both the lindane-treated seedlings and the untreated check. There was no statistically significant difference in flea beetle damage between the lindane-treated plants and the untreated check at 15 days after emergence. Although flea beetle damage was generally too low in all treated and untreated plants to allow for a meaningful assessment of performance from 23 to 42 days after emergence, 100% mortality was reported for flea beetles exposed to thiamethoxam-treated plants at 42 days after emergence.

In the other laboratory trial, mortality of caged flea beetles was measured by counting the number of dead beetles on canola seedlings following a three-day feeding period beginning one week after seeding. Thiamethoxam applied at rates of 200 and 400 g a.i./100 kg seed each resulted in 100% mortality of flea beetles. Lindane seed treatments also resulted in 100% mortality of flea beetles. Since this study was designed to show mortality activity during the first few days after plant emergence, the results do not provide information regarding the comparative residual performance of thiamethoxam and the other treatments.

Results from these growth chamber trials suggest that thiamethoxam seed treatment provides good knockdown of flea beetles and longer protection of seedlings from flea beetle damage compared with lindane seed treatments (e.g., >10 days after emergence). The submitted studies do not provide definitive results, however, regarding the duration of the residual activity of thiamethoxam when applied at 200 or 400 g a.i./100 kg seed.

Diseases

Growth chamber studies for disease control consisted of pot grown plants of several cultivars representing *Brassica rapa*, *B. napus* and *B. juncea* as well as one or more isolates of the test pathogen. All growth chamber studies were done with artificial inoculum of a single pathogen added to the potting mix except for blackleg, where the pathogen was added as a spore suspension to seed or foliage. The tests included both an infested and uninfested untreated check, Helix applied to seed at full (434 g total a.i./100 kg seed) and half (217 g) label rates, and commercial standards containing carbathiin, thiram and thiabendazole. Plants were incubated at controlled temperature and humidity and then assessed for emergence, survival and symptoms.

The effect of *Pythium* was to kill emerging seedlings in the infested check within 10 days after planting (e.g., pre- or post-emergent damping-off), often resulting in plant counts near zero. The degree of damping-off in checks varied with location and crop: mustard did not appear to be as affected as canola. Across these differences, however, treatment with Helix resulted in emergence typically within 15% of the uninoculated check, and equal to or greater than that of commercial standards. A consistent rate effect for Helix was not evident in these trials.

Inoculation with *Fusarium* did not affect initial emergence of seedlings; however, in one study, root and shoot weights were significantly reduced in the infested check compared with the uninfested check after four weeks. Dry root or shoot weight of Helix-treated seedlings was 84–108% compared with uninfested plants, whereas infested check plants were a third of this weight. In other studies, the impact of inoculum and treatment on the plant stand varied considerably with cultivar so that treatment effects could not be clearly demonstrated.

Inoculum of *Rhizoctonia solani* was added to potting mix at doses of 0.005–0.5 g/L soil in studies at one location. The main effect of this pathogen was a decline in plant stands between 7 and 28 days after planting. Disease pressure varied directly with inoculum density; moderate doses of 0.01 and 0.05–0.1 g/L were most useful for differentiating treatment effects. The relevance of inoculum dose in these trials to typical pathogen levels in the field was not discussed. Treatment with full rate of Helix maintained plant stands of 40–100% for four cultivars compared with 10–49% in the infested check at the two lower inoculum levels. Commercial standard products were typically significantly less effective than Helix or were ineffective. These data suggest that Helix maintains good plant survival in the presence of *Rhizoctonia* compared with currently available seed treatments; however, this effect is highly dependent on disease pressure and on cultivar.

In blackleg studies at one location, seeds were inoculated with a spore suspension of *L. maculans*. Plant emergence was not affected initially; however, stand declined rapidly between 7 and 35 days to less than 31% in the check. Helix treatment resulted in greater than 90% survival for four canola cultivars but mustard was less affected by the pathogen and less responsive to treatments. Mustard in general is known to be tolerant to blackleg. Helix was equivalent to or slightly more effective than commercial standards. Similar results were obtained with different cultivars at a second site where *L. maculans* was introduced by adding inoculum to the potting mix and the number of healthy seedlings

was recorded. A further study where seedlings were sprayed with *Leptosphaeria* spore suspension confirmed that Helix had no effect on foliar infection of seedlings. There was no consistent trend in product rate effects.

7.1.3.3 Small-scale field trials

Flea beetles

Results were submitted from 28 field studies conducted in Ontario, Manitoba, Saskatchewan and Alberta in 1996–2000 that assessed the performance of thiamethoxam seed treatment (Helix or Helix XTra) for the control of flea beetles on canola and mustard. In most trials, the performance of thiamethoxam treatments was compared with that of commercial lindane-based seed treatments, a combination lindane seed treatment plus in-furrow granular insecticide (terbufos) treatment, and an untreated check. Efficacy of the treatments was assessed by measuring seedling emergence, flea beetle damage to seedlings, vigour of plants, fresh weights of plants and yield at harvest.

Flea beetle populations varied considerably among the submitted trials in terms of the level and duration of flea beetle pressure. In six of the trials, very low flea beetle populations were reported to have occurred and, therefore, provided no meaningful information regarding performance against this pest. In the remaining trials with measurable levels of flea beetle pressure, thiamethoxam seed treatment applied at rates of 200 and 400 g a.i./100 kg seed significantly reduced flea beetle damage to foliage or improved seedling emergence, plant weights or vigour compared with the untreated check. Both rates of thiamethoxam provided levels of control that were equal to, or better than, the standard lindane and lindane + terbufos treatments. In trials with low to moderate flea beetle pressure, both the 200 and 400 g rates of thiamethoxam provided comparable levels of protection against flea beetle pressure. In some trials conducted under high or extended flea beetle pressures (e.g., >50% damage to foliage in the untreated check at 30–39 days after planting), however, the 400 g rate appeared to provide greater protection of seedlings than did the 200 g rate. Limited data (five trials) were submitted on the efficacy of thiamethoxam at rates lower than 200 g a.i./100 kg seed. These limited data show, however, that an application rate of 100 g thiamethoxam/100 kg seed did not perform consistently as well as did rates of 200 or 400 g thiamethoxam/100 kg seed.

The efficacy of thiamethoxam at application rates of 200 and 400 g a.i./100 kg seed was similar to that for the standard lindane seed treatments based on assessments conducted at 12–16 days after planting (cotyledon to one-leaf stage), with all treatments resulting in significantly less flea beetle damage compared with the untreated check. Thiamethoxam, at both the 200 and 400 g a.i./100 kg seed rates of application, appeared to provide longer residual protection against flea beetle damage than did lindane seed treatment. In one trial, the 200 and 400 g thiamethoxam rates provided equivalent control as did the standard lindane treatment for up to 7–10 days after emergence. At 10–15 days after emergence, the 200 g thiamethoxam rate provided significantly better control than did the standard lindane treatment (the reduction in activity of the lindane treatment by this time is consistent with the expected level of protection against flea beetles afforded by lindane-based seed-treatments, i.e., 7–10 days protection following emergence). In trials

where flea beetle populations were high and extended (e.g., >50% damage to foliage in the untreated check at 30–39 days after planting), the lindane treatments did not perform consistently as well as did the thiamethoxam treatments, based on assessments at 30–39 days after planting.

All of the submitted flea beetle trials compared the efficacy of thiamethoxam with that of a commercial lindane seed treatment in combination with a granular insecticide (terbufos) treatment. The lindane + granular standard is generally recognized as providing protection of seedlings for approximately 21 days after emergence. In trials where populations were high or extended, the 200 g thiamethoxam/100 kg seed treatment provided levels of control that were comparable to the lindane + terbufos standard, with both treatments providing significant reduction in flea beetle damage compared with the untreated check, based on assessments 30–39 days after planting. In the same trials, the 400 g thiamethoxam/100 kg seed treatment provided levels of control equivalent to, or greater than, that of the lindane + granular standard.

The label for Helix claims control of flea beetles for 14–21 days after seedling emergence and the label for Helix XTra claims 28–35 days control of flea beetles. While the submitted studies do not allow for a definitive assessment of the full period of residual activity of the two products, the data show good protection of flea beetles over the durations claimed on the label. The submitted data suggest that both products would provide good protection of seedlings against flea beetles attack over the critical three-week period after emergence.

Of the 22 trials with measurable flea beetle pressures reported, 20 assessed the impact of treatment on yield at harvest. Yield of harvested seed was statistically higher from plots receiving the 200 g thiamethoxam/100 kg treatment compared with the untreated check in 6 of 20 trials (0–100.4% increase in yield in 20 trials compared with the untreated check). Yields from plots receiving the 400 g thiamethoxam/100 kg seed treatment were statistically higher than the untreated check in 8 of 20 trials (0–119.6% increase in yield in 20 trials compared with the untreated check). The greatest increases in yield were reported in trials where flea beetle pressures were highest. Statistically, there was no significant difference in yield response among the 200 and 400 g a.i. treatments, the commercial lindane seed treatments, or the combination lindane + granular treatments.

Seven trials compared the performance of seed treated with Helix or Helix XTra prior to planting with that of seed treated the previous year and stored for one year. There was little statistical difference between these treatments in terms of emergence counts, flea beetle damage ratings or yield. This suggests that canola seed treated with Helix or Helix XTra in one year can be carried over to the next year without a loss in performance against flea beetles or diseases.

Diseases

In disease efficacy field trials in Ontario and Alberta, many variables affected emergence. Overall, plant stands were lower and the effect of introduced inoculum was much less prominent than in the controlled environment studies. In *Pythium* trials, emergence counts were reduced by up to 30% due to inoculation. The inconsistent disease pressure and variability between plots meant, however, that no meaningful trends in *Pythium* control could be determined. For some cultivars, Helix-treated seed had higher stand counts than even the *uninfested* check, suggesting insect control or overall benefits in field soil.

The effect of inoculation with *Fusarium* was less evident than in the growth chamber studies, and stand counts were significantly reduced in the infested check for only two of five cultivars. In those tests, however, Helix treatment, particularly at full rate, resulted in significantly higher counts, comparable to that of the uninfested check.

In all *Rhizoctonia* trials, plant numbers were significantly reduced by inoculation to 26–60% of uninfested check. Helix performed well at one site, improving plant stand to the same level as the uninfested check and at the other location, significantly increasing stand numbers to midway between the two checks. There was a small but consistent difference in efficacy between full and half rates of Helix.

In blackleg trials, one effect of Helix or tankmix combinations of fludioxonil, difenoconazole and metalaxyl-M was to increase emergence over the uninfested check, to give more commercially acceptable plant stands of greater than 50% emerged. Inoculation of seed apparently had little impact, however, on the level of blackleg symptoms compared with disease from inoculum already present in the field. These field studies were not able to demonstrate control of seedborne blackleg symptoms; however, they did confirm that, in general, seedling survival is improved with Helix treatment.

These data support label claims of control of seed-borne blackleg and the seedling disease complex (damping-off, seedling blight, seed rot and root rot) caused by *Pythium*, *Fusarium* and *Rhizoctonia*. While the half rate of Helix performed well in many trials and efficacy was comparable to or better than commercial standards, in some cases the full label rate appeared to provide better results. There is not sufficient evidence, therefore, that the half product rate consistently provides the lowest effective rate of fungicide.

7.2 Phytotoxicity to target plants (including different cultivars) or to target plant products

Results were provided from small-plot field trials conducted in Alberta, Saskatchewan and Manitoba in 1997–1999 that evaluated the tolerance of various canola and mustard varieties to thiamethoxam seed treatment. Twenty different varieties of canola were evaluated in 17 trials and three different varieties of mustard were evaluated in six trials. The maximum rate of application tested was 534 g total a.i./ha (500 g thiamethoxam, 2.5 g fludioxonil, 24 g difenoconazole and 7.5 g metalaxyl-M per 100 kg seed). The submitted data package states that higher rates of application were considered but would not stick to the seed and, therefore, were not tested. Crop tolerance was evaluated by

conducting assessments of seedling emergence and phytotoxicity. The performance of Helix and Helix XTra was compared with that of a commercial standard seed treatment (containing carbathiin, thiram and lindane) and an untreated check.

With the exception of the canola variety Reward in a single trial, no adverse effects on seedling emergence were reported with the Helix or Helix XTra treatments compared with the untreated check. The lower emergence counts reported for the Reward variety in one trial did not result significantly lower yield at harvest. No visual symptoms of phytotoxicity were reported with any of the treatments.

Two of the trials assessed crop tolerance following storage of treated canola seed for one year. There was no significant difference in emergence counts between seed treated with Helix XTra in the same year as planting, seed treated the previous year and stored for one year, or the untreated check. No symptoms of phytotoxicity were reported with any of the treatments.

Results from the submitted trials demonstrate good crop safety of Helix and Helix XTra to canola and mustard varieties.

7.3 Sustainability

7.3.1 Survey of alternatives

7.3.1.1 Nonchemical control practices

There are currently no canola or mustard varieties that are resistant to flea beetles. Summer fallow fields that contain volunteer canola or mustard or cruciferous weeds provide an alternate source of food for flea beetles. Delaying cultivation of these fields until after the canola crop has reached the four-leaf stage can mitigate against early-season damage caused by immigration of adult beetles into the canola field. Increasing the seeding rate in areas where flea beetle populations were high the previous fall may help mitigate against flea beetle impacts. There are no effective cultural practices, however, to control an existing high population of flea beetles.

Current management practices to limit early blackleg include long rotation to nonhost crops, volunteer plant and weed control and use of clean seed of tolerant varieties. Planting in warm soil with firm seedbed at less than 4 cm depth and use of clean seed are recommended to reduce damping-off and root rots.

7.3.1.2 Chemical control practices

Due to difficulties in predicting the expected level of flea beetle populations at the time of seeding, prophylactic treatment with chemical insecticides are the primary tools for controlling flea beetles. Lindane seed treatments generally provide control of flea beetles for about 7–10 days after seedling emergence. Imidacloprid seed treatment has recently been registered in Canada for use on canola for the control of flea beetles and provides a similar level of control as does lindane. In-furrow application of granular insecticide

(terbufos) provides longer protection than do lindane or imidacloprid seed treatments (i.e., up to 21 days after emergence). Post-emergence, foliar application of insecticides (e.g., carbofuran, deltamethrin, chlorpyrifos, malathion) is also available for the control of flea beetles on canola.

Seed treatment with fungicides (benomyl, carbathiin, iprodione, metalaxyl-M, thiabendazole or thiram) is recommended to reduce damping-off, seedling blight, seed rot and root rot. These fungicides are typically combined with an insecticide to protect the emerging crop. Propiconazole is registered for foliar application to control later blackleg symptoms.

7.3.2 Compatibility with current management practices including IPM

Current pest management practices for early-season control of diseases and flea beetles on canola and mustard involve seed treatments with fungicides and insecticides. As a seed treatment, Helix and Helix XTra are compatible with these practices.

7.3.3 Contribution to risk reduction

Lindane seed treatment and in-furrow application of granular insecticide (e.g., terbufos) have been the principal chemical options for early-season control of flea beetles on canola and mustard in Canada. Lindane is under Special Review with the PMRA (and is under international scrutiny) because of concerns regarding potential impacts to human health and the environment. Also, the use of lindane on canola and mustard in Canada presents a trade irritant issue, as lindane is not registered for these uses in the U.S. and there are no U.S. tolerances for these commodities. The PMRA is also generally concerned about the potential impacts to birds posed by granular formulations of insecticides that are toxic to wildlife (e.g., terbufos). Results from the submitted efficacy studies suggest that both Helix and Helix XTra would be alternatives to both the lindane and granular insecticide treatments currently used for early-season flea beetle control on canola and mustard in Canada.

7.3.4 Information on the occurrence or possible occurrence of the development of resistance

According to Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance Management Labelling Based on Target Site/Mode of Action*, the following statements should be incorporated on the labels for the end-use products:

Groups 3, 4, 12	**Fungicides**
Group 4	**Insecticide**

Resistance management recommendations
For resistance management, Helix (Helix XTra) contains a Group 4 insecticide and Groups 3, 4 and 12 fungicides. Any insect or fungal population may contain individuals naturally resistant to Helix and other Group 4 insecticides or Groups 3, 4 and 12 fungicides. A gradual or total loss of pest control may occur over time if these

insecticides and fungicides are used repeatedly in the same fields. Other resistance mechanisms that are not linked to site of action but are specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed.

To delay insecticide and fungicide resistance:

- Where possible, rotate the use of Helix (Helix XTra) or other Group 4 insecticides and Groups 3, 4 and 12 fungicides with different groups that control the same insects or pathogens.
- Insecticide and fungicide use should be based on an IPM program that includes scouting, historical information related to pesticide use and crop rotation and that considers cultural, biological and other chemical control practices.
- Monitor treated insect and fungal populations for resistance development.
- Contact your local extension specialist or certified crop advisors for any additional pesticide resistance-management and IPM recommendations for specific crops and pests problems in your area.
- For further information and to report suspected resistance, contact (xxx company representatives) at (toll free number) or at (Internet site).

7.4 Conclusions

Both Helix and Helix XTra seed treatments are proposed for early-season control of flea beetles on canola and mustard. The difference between these products is the proposed rate of application for thiamethoxam and the proposed claim for the control of flea beetles. The proposed application rate for Helix is 200 g thiamethoxam/100 kg seed with a label claim for the control of flea beetles for 14–21 days after seedling emergence. The proposed application rate for Helix XTra is 400 g thiamethoxam/100 kg seed with a label claim for the control of flea beetles for 28–35 days after seedling emergence.

Results from the submitted laboratory and field studies regarding the efficacy of Helix and Helix XTra compared with commercial standard treatments for early-season control of flea beetles (i.e., lindane seed treatment alone or in combination with an in-furrow application of granular insecticide) show the following:

- Both Helix and Helix XTra provided very good and consistent early-season control of flea beetles on canola and mustard.
- Both Helix and Helix XTra provided longer residual activity against flea beetles compared with commercial lindane seed treatments, which typically provide protection of seedlings for 7–10 days after emergence.

- The performance of Helix was comparable to that of the commercial standard lindane + granular insecticide treatment, whereas Helix XTra performed as well as or better than (i.e., provided protection of seedlings for longer duration) the lindane + granular standard, especially under conditions of high and extended flea beetle pressure. The commercial standard lindane + granular insecticide treatment typically provides protection of seedlings for up to 21 days after emergence.

- Although the submitted data do not allow for a definitive assessment of the residual activity of Helix and Helix XTra, the data suggest that each product provides protection of seedlings from flea beetle damage for the durations proposed on the label.

- Both products provided good protection of seedlings against flea beetle damage over the three-week period after seedling emergence.

- Under conditions of very high flea beetle pressure or prolonged attack, Helix XTra appeared to provide better control (i.e., protection of seedlings for longer duration) than did Helix or the standard lindane + granular treatment.

Although the submitted efficacy data suggest that Helix XTra provides longer protection from flea beetle attack than does Helix, statistically there was little difference in the performance of the two products under the conditions encountered in most trials. Both formulations provided good protection of seedlings over the critical three-week period after seedling emergence when the crop is generally most susceptible to losses from flea beetle damage. Results from the submitted studies show that the performance of Helix was comparable to that of the combination lindane + granular insecticide treatment, which is the commercial standard for extended early-season flea beetle control. Although a difference in residual performance between Helix and Helix XTra was apparent in some trials, the merit of the added performance of Helix XTra over Helix, with respect to the management of flea beetles and crop production, was not evident from the submitted trials.

Adequate efficacy data have been submitted to support Helix. Further information is required, however, to support the merit of Helix XTra. This information must include a rationale, supported by efficacy data, that supports the merit of the extended protection of seedlings provided by Helix XTra compared with Helix (e.g., beyond three weeks after seedling emergence) with respect to the objectives for management of flea beetle damage and crop production. If the rationale supporting Helix XTra includes being a replacement for currently available commercial treatments (e.g., seed treatments, in-furrow granule treatment, foliar treatments, either alone or in combination), the efficacy studies must allow for a direct comparison of the relative performance of Helix and Helix XTra with these treatments.

The efficacy of Helix against soil and seedborne diseases was evaluated on a range of canola cultivars and one mustard cultivar. Controlled environment trials demonstrated that Helix maintains good emergence and plant stand in the presence of *Pythium*, *Fusarium*, seedborne *L. maculans*, and *R. solani* for up to five weeks. Helix had no activity against foliar infection by *L. maculans*. Helix performed well in field trials, and the effect on emergence was comparable to or better than that of commercial standards.

Submitted crop tolerance studies with Helix and Helix XTra support good crop safety of these products to canola and mustard.

Submitted studies support the claim that treated seed can be carried over to the following year without a loss in efficacy or crop safety.

8.0 Toxic Substances Management Policy considerations

During the review of Helix Seed Treatment, the PMRA has considered the implications of the federal TSMP[1] and the PMRA Regulatory Directive DIR99-03 and has concluded the following.

- Thiamethoxam does not meet the criteria for persistence. Its value for half-life in soil (111 days) is below the TSMP Track-1 cut-off criteria for soil (≥182 days).
- Thiamethoxam is not bioaccumulative. Studies have shown that the log K_{ow} is –0.13, which is below the TSMP Track-1 cut-off criterion of ≥5.0.
- Thiamethoxam does not meet the criteria for CEPA-toxic or CEPA-toxic equivalent under the TSMP.
- Thiamethoxam does not contain any by-products or microcontaminants. Impurities of toxicological concerns are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.
- The formulated product does not contain any formulants that are known to contain TSMP Track-1 substances.

9.0 Regulatory decision

Thiamethoxam Technical and the end-use products Helix and Helix XTra have been granted temporary registrations for use on canola and mustard, pursuant to Section 17 of the Pest Control Product Regulations, subject to the following conditions:

- submission of postnatal developmental neurotoxicity study with thiamethoxam;

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1 The federal Toxic Substances Management Policy is available through Environment Canada's Web site at: www.ec.gc.ca/toxics.

- submission of further information supporting the merit of Helix XTra compared with Helix; and

- implementation of a Product Stewardship Program for Helix XTra that consists of the following elements: training, glove provision, restrictions on the label regarding the use of compressed air for cleaning, on-site stewardship and appropriate feedback mechanisms.

List of abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
AlkP	alkaline phosphatase
ALT	alanine aminotransferase
ARfD	acute reference dose
AST	aspartate aminotransferase
BrdU	bromodeoxyuridine
BROD	benzyloxyresorufin-*O*-debenzylase
bw	body weight
CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50%
EC_{25}	effective concentration 25%
EEC	expected environmental concentration
EPA	U.S. Environmental Protection Agency
EROD	ethoxyresorufin-*O*-deethylase
FOB	functional observational battery
F_0	parental animals
F_1	1st generation offspring
F_2	2nd generation offspring
GC	gas chromatography
h	hour(s)
HPLC–UV	high performance liquid chromatography with UV detection
ILV	interlaboratory validation
K_{ow}	*n*-octanol–water partition coefficient
K_d	adsorption quotient
K_{oc}	adsorption quotient normalized to organic carbon
LC	liquid chromatography
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LMA	locomotor activity
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
MCH	mean corpuscular hemoglobin
MIS	maximum irritation score
MAS	maximum average score (at 24, 48 and 72 h)
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
n	number
nm	nanometre
NOAEL	no observed adverse effect level
NOEC	no observable effect concentration
NOEL	no observable effect level

NPD–GC	nitrogen–phosphorus detection – gas chromatography
NZW	New Zealand White
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
PROD	pentoxyresorufin-*O*-depentylase
Q_1^*	linear default value (cancer estimate risk number)
RNA	ribonucleic acid
ROC	residue of concern
SD	Sprague–Dawley
$t_{½}$	half-life
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
μg	micrograms
μL	microlitre

Appendix I Method of analysis

Table 1 Methods for analysis of the active substance as manufactured

Product	Analyte	Method	Recovery	Standard deviation	Method acceptability
Technical	thiamethoxam	HPLC–UV	not required	0.35%	acceptable
	impurities	HPLC–UV	80–107%	3.4–6.1%	acceptable

Table 2 Method for formulation analysis

Product	Analyte	Method	Mean recovery (%)	Standard deviation	Method acceptability
Helix XTra	thiamethoxam	HPLC–UV at 220 nm (Method ID: AF-1333/1)	100.5 (n = 3)	1.6 (n = 5)	acceptable
	metalaxyl-M		101 (n = 3)	0.32 (n = 5)	
	fludioxonil		100 (n = 3)	1.6 (n = 5)	
	difenoconazole		102 (n = 3)	0.38 (n = 5)	
Helix	thiamethoxam	HPLC–UV at 220 nm (Method ID: AF-1414/1)	98.4 (n = 2)	0.33 (n = 5)	acceptable
	metalaxyl-M		97.9 (n = 2)	0.29 (n = 5)	
	fludioxonil		93.3 (n = 2)	1.19 (n = 5)	
	difenoconazole		100 (n = 2)	0.0 (n = 5)	

Table 3 Methods for residue analysis

Multiresidue methods for residue analysis
Thiamethoxam could not be quantified by accepted multiresidue methods.

Methods for residue analysis of plants and plant products
Data gathering method: AG-675
HPLC–UV or MS NPD–GC (Limit of quantitation (LOQ): 0.01 ppm for parent and metabolite CGA 322704)

Residue of concern (ROC): parent and metabolite CGA 322704 namely 3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-*N*-nitro-4*H*-1,3,5-oxadiazin-4-imine and the metabolite 1-(2-chloro-triazol-5-ylmethyl)-3-methyl-*N*-nitro-guanidine

Method validation
Numbers outside the acceptable range of 75–120% are reported as individual values.

Commodity	Fortification level (ppm)	% Recovery (n)			
		Parent	Mean	CGA 322704	Mean
Canola seed	0.05–0.5	62, 75–101 (5)	85	68, 76–99 (5)	84
	0.025–0.5	64, 73–105 (8)	83	61, 67, 71–113 (7)	87

Mustard seed	0.05–0.5	114–120 (4), 123, 123	119	86–110 (6)	102
Concurrent method recoveries					
Canola seed	0.01–0.5	76–106 (6)	91	75–103 (6)	88
	0.15–0.5	47, 86	67	62, 85	74
	0.025–0.15	66, 78–105	84	74–119 (4), 121	108
Mustard seed	0.05–0.5	84–118 (4)	98	78–98 (4)	92

Confirmatory method
HPLC–MS or MS–MS
Recoveries were acceptable

Enforcement method
Enforcement method equivalent to data gathering method

Interlaboratory validation (ILV)
Interlaboratory validation indicated good reliability and reproducibility

Analytical method: animal matrices
Data gathering method: AG-675
HPLC–UV or MS NPD–GC (LOQ: 0.01 ppm for parent and metabolite CGA 322704)

ROC: parent and metabolite CGA 322704 namely 3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-*N*-nitro-4*H*-1,3,5-oxadiazin-4-imine and the metabolite 1-(2-chloro-triazol-5-ylmethyl)-3-methyl-*N*-nitro-guanidine

Commodity	**Fortification level (ppm)**	**% Recovery (*n*)**			
		Thiamethoxam	**Mean**	**CGA 322704**	**Mean**
Cow, fat, omental	0.01–2.0	79.1–86.3 (5)	82.8	85.2–90.0 (50)	86.8
Cow, kidney	0.01–1.0	82.8–91.4 (4)	86.2	87.0–94.4 (4)	89.6
Cow, liver	0.01–0.5	84.3–90.1 (5)	86	86.0–91.6 (5)	89.3
Goat, milk	0.005–0.5	87.8–112.6 (3)	101.5	89.7–95.9 (3)	93.8
Goat, muscle	0.01–1.0	86.0–88.1 (3)	86.7	88.1–89.1 (3)	88.5
Poultry, eggs	0.01–2.0	81.2–91.9 (4)	85	85.4–94.8 (4)	89.3
Poultry, fat	0.01–1.0	83.8–97.9 (5)	88.5	89.2–94.0	92.6

Confirmatory method
HPLC–MS or MS–MS
Recoveries were acceptable

Enforcement method
Enforcement method equivalent to data gathering method

ILV
Interlaboratory validation indicated good reliability and reproducibility

Appendix II Toxicology summary tables

Table 1 Summary of the toxicity studies with thiamethoxam

Metabolism

Rate and extent of absorption and excretion: Rapidly absorbed and eliminated in rats and mice. Absorption, distribution metabolism and excretion were independent of sex, dose, pretreatment and position of the radiolabel. Similar routes of transformation were observed in rats and mice. **Rats**: Blood concentrations peaked at 4 h, followed by rapid elimination. Approximately 84–95% of the dose was excreted in the urine and 2.5–6% was excreted in the faeces within 24 h. Less than 0.2% of the dose was detected in expired air. Approximately 20–30% of the dose was biotransformed. **Mice**: Approximately 72% of the dose was excreted in the urine and 19% was excreted in the faeces. A small amount was detected in expired air (0.2%). Approximately 30–60% of the dose was biotransformed.

Distribution and target organ(s): Widely distributed to the tissues, with the highest concentrations detected in skeletal muscle within 8 h of dosing, accounting for 10–15% of the administered dose. Tissue half-times of elimination ranged from 2 to 6 h. After 7 days, tissue residues were all very low, with the highest amounts detected in liver (0.01–0.04% of the dose).

Toxicologically significant compound(s): Only three urinary metabolites accounted for greater than 1–2% of the administered dose in rats. Unchanged parent CGA 293343 accounted for 69–83% in rats (31–44% in mice); CGA 322704 was the major urinary metabolite in rats (5–13% of the dose) and mice (8–12% of the dose). The acute oral LD_{50} of CGA 322704 was greater than 2000 mg/kg in Wistar rats. CGA 265307 accounted for 1–2% of the dose in rats and 9–18% of the dose in mice.

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Acute studies: Technical			
Oral	Rat, Crj:CD(SD) SPF 0, 900, 1500, 2300, 2800 or 6000 mg/kg	LD_{50} = 1563 mg/kg	**Sightly toxic**, All deaths occurred within 6 h of dosing. Clinical signs noted on the day of dosing included ptosis, decrease in spontaneous movement and tonic convulsions. Body weight gain was retarded for 2 days following dosing (all treated animals).
Oral	Mouse, Crj:CD-1 (ICR) SPF 0, 500, 700, 1000, 1400 or 2000 mg/kg	LD_{50} = 871 mg/kg	**Moderately toxic**, All deaths occurred within 1 day of dosing. Clinical signs noted on the day of dosing included clonic convulsion, decrease in spontaneous movement or prone position. Body weight gain was retarded in surviving ♀ on the day following dosing.
Dermal	Rat, Crj:CD(SD) SPF 2000 mg/kg	LD_{50} > 2000 mg/kg	**Low toxicity**, No mortality, no adverse clinical signs and no effect on body weight.
Inhalation	Rat, Crj:CD(SD) SPF 1.02 or 3.72 mg/L	LC_{50} > 3.72 mg/L	**Low toxicity**, No mortality, no treatment-related clinical signs. Slight body weight decreases noted in 2 high-dose ♀ on day 7, recovered by day 14.
Eye irritation	Rabbit, Japanese White 0.1 g	Maximum average score (MAS) = 0 Maximum irritation score (MIS) = 10.0 (1 h)	**Minimally irritating**, Slight conjunctival redness and swelling observed at 1 h, with eye closure and more than normal discharge. All signs of irritation absent at 24 h.

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Skin irritation	Rabbit, Japanese White 0.5 g	MAS = 0 MIS = 0	**Nonirritating**, No signs of irritation in any of the animals tested.
Skin sensitization (Maximization Test)	Guinea pig, Pirbright White, Tif:DHP	Nonsensitizing	**Nonsensitizing**, No evidence of sensitization.
Acute studies: Helix			
Oral	Rat, Crl:CD(SD)BR 5000 mg/kg	LD_{50} > 5000 mg/kg	**Low toxicity**, No mortality, no clinical signs and no effect on body weight.
Dermal	Rabbit, New Zealand White (NZW) 2000 mg/kg	LD_{50} > 2000 mg/kg	**Low toxicity**, No mortality, no clinical signs and no effect on body weight. Slight dermal irritation observed in 6/10 animals, cleared by day 6.
Inhalation	Rat, HSD: Sprague–Dawley (SD) 2.67 mg/L	LC_{50} > 2.67 mg/L	**Low toxicity**, No mortality. Clinical signs included activity decrease, piloerection and blue staining of the face, signs cleared by day 3.
Eye irritation	Rabbit, NZW 0.1 mL	MAS = 0.2 MIS = 9.0 (unwashed eyes, 1 h)	**Minimally irritating**, in both washed and unwashed eyes, iridal irritation observed in one animal and slight to moderate conjunctival irritation in all three animals. All signs of irritation absent at 24 h (washed) or 48 h (unwashed).
Skin irritation	Rabbit, NZW 0.5 mL	MAS = 0 MIS = 0	**Nonirritating**, No signs of irritation in any of the animals tested.
Skin sensitization (Buehler Test)	Guinea pig, Crl:HA(BR)	Nonsensitizing	**Nonsensitizing**, No evidence of sensitization.
Acute studies: Helix XTra			
Oral	Rat, Crl:CD(SD)BR 5000 mg/kg	LD_{50} > 5000 mg/kg	**Low toxicity**, One ♀ died within 2.5 h of dosing. No clinical signs noted in ♂. Clinical signs noted in ♀ on the day of dosing included hypoactivity, staggered gait, hunched posture, cold to touch and tremors.
Dermal	Rabbit, NZW 2000 mg/kg	LD_{50} > 2000 mg/kg	**Low toxicity**, No mortality and no clinical signs. Slight to moderate irritation noted at application site, persisting for 5–8 days.
Inhalation	Rat, HSD: SD 0.773 or 2.56 mg/L	LC_{50} > 2.56 mg/L	**Low toxicity**, No mortality and no clinical signs at either concentration.
Eye irritation	Rabbit, NZW 0.1 mL	MAS = 0.5 MIS = 4.0 (washed eyes, 1 h)	**Minimally irritating**, Slight conjunctival irritation observed in washed and unwashed eyes, absent at 48 h in unwashed and 72 h in washed eyes.
Skin irritation	Rabbit, NZW 0.5 mL	MAS = 0.6 MIS = 0.7 (4 h)	**Slightly irritating**, Very slight erythema and edema noted in 2 animals, with desquamation in 1 at 72 and 96 h, all signs of irritation absent at 7 days.

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Skin sensitization (Buehler Test)	Guinea pig, Crl:HA(BR)	Nonsensitizing	**Nonsensitizing**, No evidence of sensitization.
Short-term toxicity			
28-d gavage	♂ Rat, Tif:RAIf (SPF), 5/sex/dose at 0, 100, 300, 1000 mg/kg bw/d	No NOAEL: dose range-finding study only.	Very scant information reported, study conducted for range-finding purposes only 100 mg/kg bw/d and above: hyaline change of renal tubular epithelium (not present in high-dose animals) 300 mg/kg bw/d and above: ↑ liver weight, dilatation of renal pelvis, hepatocellular hypertrophy, ↑adrenocortical fatty change 1000 mg/kg bw/d: ↓bw gain, ↓plasma protein, ↑aspartate aminotransferase (AST), alkaline phosphatase (AlkP) and gamma glutamyl transpeptidase, ↓thymus weight
28-d dietary	Rat, Tif:RAIf (SPF), 5/sex/dose at 0, 100, 1000, 2500 or 10000 ppm (♂ = 0, 8.0, 82, 199 or 711 mg/kg bw/d, ♀ = 0, 8.7, 89, 211 or 763 mg/kg bw/d)	NOAEL = 100 ppm (8.0/8.7 mg/kg bw/d, ♂/♀) LOAEL = 1000 ppm (81.7/89.3 mg/kg bw/d, ♂/♀)	1000 ppm and above: hyaline change of renal tubular epithelium (♂, not present in high-dose animals), basophilic proliferation of renal tubules (incidence dropped at high dose) 2500 ppm and above: hepatocellular hypertrophy, hypertrophy of thyroid follicular epithelium (♂) 10000 ppm: ↓bw gain and food consumption (♂), ↑cholesterol, AST (♂), absolute and relative liver weight, dilatation of renal pelvis, fatty change of adrenal cortex, hypertrophy of thyroid follicular epithelium (♀)
28-d dietary	Beagle Dogs, 2/sex/dose at 0, 300, 1000 or 3000 ppm (♂ = 0, 10.0, 31.6 or 47.7 mg/kg bw/d, ♀ = 0, 10.7, 32.6 or 43.0 mg/kg bw/d)	NOAEL = 1000 ppm (31.6/32.6 mg/kg bw/d, ♂/♀) LOAEL = 3000 ppm (47.7/43.0 mg/kg bw/d, ♂/♀)	3000 ppm: ↓food consumption, ↓body weight, leukopenia, ↑hematocrit, hemoglobin and erythrocytes (♂), ↑urea, ↑creatinine, ↓thymus weight (♂/♀), ↑thyroid weight (♂), ↓brain weight (♀), histopathology in liver, thymus and spleen Note: 1 high-dose ♂ died on day 15, due to blockage of small intestine (unrelated to treatment)
28-d dermal	Rat, Tif:RAIf (SPF), 5/sex/dose at 0, 20, 60, 250 or 1000 mg/kg bw/d	NOAEL = 60 mg/kg bw/d (♀) NOAEL = 250 mg/kg bw/d (♂) LOAEL = 250 mg/kg bw/d (♀) LOAEL = 1000 mg/kg bw/d (♂)	250 mg/kg bw/d and above: ↑glucose, AlkP and triglyceride (♀), histopathology findings in ♀: inflammatory cell infiltration in the liver, hepatocellular degeneration, chronic tubular lesions in the kidneys, and inflammatory cell infiltration in the adrenal cortex 1000 mg/kg bw/d: slight ↓bw (♂), hyaline change in renal tubules (♂)

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
90-d dietary	Rat, Tif:RAIf (SPF), 10/sex/dose at 0, 25, 250, 1250, 2500 or 5000 ppm (♂ = 0, 1.7, 17.6, 84.9, 168 or 329 mg/kg bw/d, ♀ = 0, 1.9, 19.2, 92.5, 182 or 359 mg/kg bw/d)	NOAEL = 25 ppm (1.7 mg/kg bw/d, ♂) NOAEL = 1250 ppm (92.5 mg/kg bw/d, ♀) LOAEL = 250 ppm (17.6 mg/kg bw/d, ♂) LOAEL = 2500 ppm (182 mg/kg bw/d, ♀)	250 ppm and above: ↑hyaline change in renal tubular epithelium (♂), ↑incidence of chronic tubular lesions (♂) 1250 ppm and above: ↓body weight, body weight gain and food consumption (♂), ↑creatinine, urea, cholesterol and platelets (♂), ↑acute renal tubular lesions and basophilic proliferation (♂) 2500 ppm and above: ↑hepatocellular hypertrophy (♂), ↑incidence of chronic renal tubular lesions and ↑severity of nephrocalcinosis (♀), ↑adrenal fatty change (♀) 5000 ppm: slight ↑platelets (♂), ↑absolute adrenal weight (♂), ↑liver, kidney, adrenal, heart and spleen weight relative to body weight (♂), ↓absolute heart and thymus weight (♀), ↑hepatocellular hypertrophy (♀), ↑Kupffer cell pigmentation (♀), ↑renal cast formation and extramedullary hematopoiesis in spleen (♂) **Control terminal body weight:** ♂: 528.7 g; ♀: 263.6 g **Control terminal daily food consumption:** ♂: 25.5 g; ♀: 16.7 g
90-d dietary	Mouse, Tif:MAGf (SPF), 10/sex/dose at 0, 10, 100, 1250, 3500 or 7000 ppm (♂ = 0, 1.4, 14.3, 176, 543 or 1335 mg/kg bw/d, ♀ = 0, 2.0, 19.2, 231, 626 or 1163 mg/kg bw/d)	NOAEL = 10 ppm (1.4 mg/kg bw/d, ♂) NOAEL = 100 ppm (19.2 mg/kg bw/d, ♀) LOAEL = 100 ppm (14.3 mg/kg bw/d, ♂) LOAEL = 1250 ppm (231 mg/kg bw/d, ♀)	100 ppm and above: hepatocellular hypertrophy (♂) 1250 ppm and above: ↓absolute and relative kidney weight (♂), ↑absolute and relative liver weight (♀), hepatocellular hypertrophy (♀) 3500 ppm and above: ↓absolute and relative ovary and absolute spleen weight (♀), ovarian atrophy, necrosis of single hepatocytes (♀), lymphocytic infiltration in liver and Kupffer cell pigmentation (♂/♀) 7000 ppm: ↓erythrocytes, hemoglobin and hematocrit, with ↑mean corpuscular volume and mean corpuscular hemoglobin (MCH) (♂), ↓body weight (♂) and body weight gain (♂/♀), necrosis of single hepatocytes (♂), organ weight changes attributed to reduced body weight development **Control terminal body weight:** ♂: 49.62 g; ♀: 31.84 g **Control terminal daily food consumption:** ♂: 6.6 g; ♀: 6.7 g

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
90-d dietary	Beagle Dogs, 4/sex/dose at 0, 50, 250, 1000 or 2500/2000 ppm (♂ = 0, 1.6, 8.2, 32 or 55 mg/kg bw/d, ♀ = 0, 1.8, 9.3, 34 or 51 mg/kg bw/d)	NOAEL = 250 ppm (8.2/9.3 mg/kg bw/d, ♂/♀) LOAEL = 1000 ppm (32/34 mg/kg bw/d, ♂/♀)	1000 ppm and above: ↑prothrombin times, ↓albumin, A/G ratio, ↓ALT (♂/♀), ↓calcium (♀), ↓cholesterol and phospholipid (♂) 2500/2000 ppm: ↓food consumption, body weight loss, dose reduced to 2000 ppm, animals fed control diets days 19–25, treatment resumed at 2000 ppm for remainder of study, ↓body weight gain and food consumption (♂/♀), microcytic anemia, leukopenia (♀), ↓monocytes, MCH and ↑hemoglobin distribution width, ↓testis and ovary weights associated with histopathological evidence of delayed maturation in ovaries and reduced spermatogenesis with minimal to moderate occurrence of spermatic giant cells in testes
12-month dietary	Beagle Dogs, 4/sex/dose at 0, 25, 150, 750 or 1500 ppm (♂ = 0, 0.7, 4.1, 21 or 42 mg/kg bw/d, ♀ = 0, 0.8, 4.5, 25 or 45 mg/kg bw/d)	NOAEL = 150 ppm (4.1/4.5 mg/kg bw/d, ♂/♀) LOAEL = 750 ppm (21/25 mg/kg bw/d, ♂/♀)	750 ppm and above: transient ↓in food consumption (♀) ↑creatinine, occasionally accompanied by ↑urea, ↓ALT, atrophy of seminiferous tubules 1500 ppm: transient body weight loss (♀), ↓testis weight, ↓prothrombin activity (♂), ↓albumin (♀)

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Chronic toxicity and oncogenicity			
78-week dietary	Mouse, Tif:MAGf (SPF), 60/sex/dose, plus 10/sex control and high dose for interim sacrifice at 9 months at 0, 5, 20, 500, 1250, 2500 ppm (♂ = 0, 0.7, 2.6, 64, 162 or 354 mg/kg bw/d, ♀ = 0, 0.9, 3.7, 88, 215 or 479 mg/kg bw/d)	NOAEL = 20 ppm (2.6/3.7 mg/kg bw/d, ♂/♀) LOAEL = 500 ppm (64/88 mg/kg bw/d, ♂/♀)	500 ppm and above: ↑relative liver weight (♀), ↑incidence of hepatocellular adenoma, ↑non-neoplastic liver histopathology including hepatocellular hypertrophy, foci of cellular alteration, necrosis of single hepatocytes, increased mitotic activity, inflammatory cell infiltration, pigment deposition (♂/♀) and Kupffer cell hyperplasia (♂) 1250 ppm and above: ↑absolute and relative liver weight, ↑hepatocellular adenocarcinoma (♀) 2500 ppm: ↓body weight gain (♂/♀), ↑hepatocellular adenocarcinoma (♂), extramedullary hematopoiesis in spleen, epithelial hyperplasia in glandular stomach **Interim sacrifice**: ↑non-neoplastic liver histopathology including hepatocellular hypertrophy, necrosis of single hepatocytes, inflammatory cell infiltration and Kupffer cell pigmentation. ↑in the number of animals with multiple tumours; however, no difference in latency of tumour formation nor in lethality from observed tumours between treated and control groups
2-year dietary	Rat, Tif:RAIf (SPF), 80/sex/dose at 0, 10, 30, 500 or 1500 ppm (♂) and 0, 10, 30, 1000 or 3000 ppm (♀) (50 main study, 10 interim sacrifice, 10 hematology and clinical chemistry and 10 hematology) (♂ = 0, 0.4, 1.3, 21 or 63 mg/kg bw/d, ♀ = 0, 0.5, 1.6, 50 or 155 mg/kg bw/d)	NOAEL = 500 ppm (21 mg/kg bw/d, ♂) NOAEL = 1000 ppm (50 mg/kg bw/d, ♀) LOAEL = 1500 ppm (63 mg/kg bw/d, ♂) LOAEL = 3000 ppm (155 mg/kg bw/d, ♀)	500 ppm (♂): ↑incidence of regenerative kidney lesions at interim sacrifice that were not observed at terminal sacrifice (chronic tubular lesions and basophilic proliferation of renal tubules) 1500 ppm (♂): slight ↑water consumption, ↑incidence of lymphocytic infiltration of renal pelvis (interim sacrifice), ↑incidence of lymphocytic infiltration in kidneys and chronic nephropathy (terminal sacrifice) 3000 ppm (♀): ↓body weight gain, slight ↑in severity of hemosiderosis of spleen at interim sacrifice, ↑incidence of foci of cellular alteration in liver, ↑incidence of chronic tubular lesions in kidneys No evidence of oncogenicity in ♂ or ♀; however, evidence suggests that ♂ could have tolerated higher doses

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Reproduction and developmental toxicity			
Range finding reproduction	Rat, Tif:RAIf (SPF), 15/sex/dose at 0, 1000, 2000 or 4000 ppm (♂ = 0, 67, 126 or 241 mg/kg bw/d, ♀ = 0, 75, 136 or 275 mg/kg bw/d)	No NOAEL or LOAEL established by the study author	1000 ppm and above: ↓body weight gain during premating period (♀) 2000 ppm and above: ↓food consumption during premating period 4000 ppm: ↓body weight gain during premating period (♂/♀) and in ♀ during lactation
Multi-generation reproduction	Rat, Tif:RAIf (SPF), 30/sex/dose at 0, 10, 30, 1000 or 2500 ppm (♂ = 0, 0.6, 1.8, 61 or 158 mg/kg bw/d, ♀ = 0, 0.8, 2.4, 79 or 202 mg/kg bw/d)	**Parental systemic** NOAEL, ♂ = 30 ppm (0.6 mg/kg bw/d) ♀ = 2500 ppm (202 mg/kg bw/d, highest dose tested) LOAEL, parental ♂ = 1000 ppm (61 mg/kg bw/d) **Offspring** NOAEL = 1000 ppm (61/79 mg/kg bw/d, ♂/♀) LOAEL = 2500 ppm (158/202 mg/kg bw/d, ♂/♀) **Reproductive** NOAEL = 10 ppm (0.6 mg/kg bw/d) LOAEL = 30 ppm (1.8 mg/kg bw/d)	30 ppm and above: ↑incidence and severity of tubular atrophy in testes of F_1 1000 ppm and above: ↑incidence of hyaline change in renal tubules (F_0 and F_1 ♂) and renal tubular casts (F_0 ♂) 2500 ppm: slight ↓parental body weight gain (F_0 and F_1 ♂), ↓pup body weight gain (all litters) during the lactation period, ↑incidence of renal tubular casts and ↓testis weight (F_1 ♂), hyaline change in renal tubules in one F_1 ♀ Equivocal results in sperm motility (decreased at all doses tested, with no apparent dose-relationship), evaluated further in a separate, complementary study that revealed no effect of treatment on sperm motility; however, the study was conducted only on F_0 animals, whereas seminiferous tubule atrophy was observed in F_1 No treatment-related adverse effects on reproductive indices (mating, gestation, fertility, viability) **Evidence of sensitivity of young** (testis effects observed only after in utero and postnatal exposure)
Range finding developmental toxicity	Rat, Tif:RAIf (SPF), 8 pregnant ♀/dose at 0, 10, 100, 500 or 1000 mg/kg bw/d from days 6 to 15 of gestation	NOAEL (maternal) = 100 mg/kg bw/d LOAEL (maternal) = 500 mg/kg bw/d NOAEL (developmental) = 500 mg/kg bw/d LOAEL (developmental) = 1000 mg/kg bw/d	500 mg/kg bw/d and above: ↓maternal body weight gain during the first half of the dosing period, ↓food consumption during the dosing period 1000 mg/kg bw/d: net loss in body weight during the first half of the dosing period, clinical signs of toxicity during the dosing period (piloerection, hypoactivity, hunched posture), ↓fetal body weight No evidence of teratogenicity

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Developmental toxicity	Rat, Tif:RAIf (SPF), 24 pregnant ♀/dose at 0, 5, 30, 200 or 750 mg/kg bw/d from days 6 to 15 of gestation	NOAEL (maternal) = 30 mg/kg bw/d LOAEL (maternal) = 200 mg/kg bw/d NOAEL (developmental) = 200 mg/kg bw/d LOAEL (developmental) = 750 mg/kg bw/d	200 mg/kg bw/d and above: ↓maternal body weight gain during the first half of the dosing period, ↓food consumption during the dosing period, ↑incidence of transient, reversible, nonadverse skeletal variations (poor ossification of specific digits) 750 mg/kg bw/d: net loss in body weight during the first half of the dosing period, clinical signs of toxicity during the dosing period (piloerection, hypoactivity, regurgitation of test material), ↓fetal body weight, ↑incidence of skeletal anomalies (asymmetrically shaped sternebrae 6 and irregular ossification of the occipital bone) No evidence of teratogenicity
Range finding developmental toxicity	Rabbit, Russian Chbb:HM, 8 pregnant ♀/dose at 0, 10, 50, 150 or 500 mg/kg bw/d from days 7 to 19 of gestation	NOAEL (maternal) = 10 mg/kg bw/d LOAEL (maternal) = 50 mg/kg bw/d NOAEL (developmental) = 50 mg/kg bw/d LOAEL (developmental) = 150 mg/kg bw/d	50 mg/kg bw/d and above: ↓body weight gain and food consumption during the dosing period 150 mg/kg bw/d: net loss in body weight during the dosing period, ↓mean gravid uterus weight, ↓fetal body weight 500 mg/kg bw/d: all animals died between study days 10 and 16 No evidence of teratogenicity
Developmental toxicity	Rabbit, Russian Chbb:HM, 19 pregnant ♀/dose at 0, 5, 15, 50 or 150 mg/kg bw/d from days 7 to 19 of gestation	NOAEL (maternal) = 50 mg/kg bw/d LOAEL (maternal) = 150 mg/kg bw/d NOAEL (developmental) = 50 mg/kg bw/d LOAEL (developmental) = 150 mg/kg bw/d	50 mg/kg bw/d: slight ↓in food consumption during the dosing period 150 mg/kg bw/d: 3 unscheduled deaths, hemorrhagic uterine contents, hemorrhagic discharge in the perineal area, net loss in body weight during the dosing period, ↓food consumption during the dosing period, ↓fetal body weight, ↑postimplantation loss, slight ↑in the incidence of skeletal anomalies and variations (fused or asymmetrically shaped sternebrae, not statistically significant; only slightly higher than range of historical control) No evidence of teratogenicity

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Neurotoxicity			
Acute neurotoxicity	Rat, Crl CD SD BR, 10/sex/dose at 0, 100, 500 or 1500 mg/kg bw	NOAEL = 100 mg/kg bw LOAEL = 500 mg/kg bw	500 mg/kg bw and above: FOB and LMA findings including drooped palpebral closure, ↓rectal temperature, ↑forelimb grip strength and ↓LMA 1500 mg/kg bw: 3 deaths (days 1 or 2), FOB and LMA findings including abnormal body tone, ptosis, impaired respiration, tremors, ↑latency to first step in open field, crouched-over posture, impaired gait, hypo-arousal, uncoordinated landing in righting reflex test, slight lacrimation (♀ only), ↑mean average input stimulus in auditory startle response (♂ only) There were no treatment-related histopathological findings noted in the central or peripheral nervous system
Subchronic neurotoxicity	Rat, Crl CD SD BR, 10/sex/dose at 0, 10, 30, 500 or 1500 ppm (♂) and 0, 10, 30, 1000 or 3000 ppm (♀) (♂ = 0, 0.7, 1.9, 32 or 95 mg/kg bw, ♀ = 0, 0.7, 2.1, 73 or 216 mg/kg bw/d)	NOAEL = 1500 ppm (95 mg/kg bw/d, ♂) NOAEL = 3000 (216 mg/kg bw/d, ♀)	There were no treatment-related systemic or neurological effects observed at any dose in this study.

Genotoxicity		
Study	**Species or strain or cell type and concentrations or doses employed**	**Results**
Gene mutations in bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537; *E. Coli* WP2uvrA 312.5–5000 μg/plate	Negative
Gene mutations in mammalian cells in vitro	Chinese hamster cells V79 61.67–2220 μg/mL without activation 123.33–3330 μg/mL with activation	Negative
Unscheduled DNA synthesis	Primary rat hepatocytes, isolated from Tif:RAIf (SPF) rats 13.01–1665 μg/mL	Negative
Chromosome aberrations	Chinese hamster ovary cells CCL 61 283.75–2270 μg/mL without activation 1135–4540 μg/mL with activation	Negative
Micronucleus assay (in vivo)	♂ and ♀ Tif:MAGf (SPF) mice 0, 312.5, 625, 1000 or 1250 mg/kg	Negative

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Special studies			
Effects on biochemical parameters in the liver	Mouse, Tif:MAGf (SPF), 6/sex/dose at 0, 100, 500 or 2500 ppm (♂ = 0, 17, 74 or 367 mg/kg bw/d, ♀ = 0, 20, 92 or 486 mg/kg bw/d)	N/A	100 ppm: slightly ↑pentoxyresorufin-*O*-depentylase (PROD) and benzyloxyresorufin-*O*-debenzylase (BROD) activity (♀) 500 ppm: ↑PROD and BROD activity (♂/♀), slightly ↑ethoxyresorufin-*O*-deethylase (EROD) (♀) 2500 ppm: slight ↑absolute and relative liver weights (♂/♀), slight ↑microsomal protein content in liver (♀), moderate ↑in cyt P450 content, slight to moderate ↑in activity of several microsomal enzymes and cytosolic glutathione-S-transferase
Assessment of hepatic cell proliferation	Mouse, Tif:MAGf (SPF), 25/sex/dose, 5/dose sacrificed on study days 3, 7, 13, 27 or 59, at 0, 100, 500 or 2500 ppm (♂ = 0, 16, 72 or 386 mg/kg bw/d, ♀ = 0, 20, 87 or 463 mg/kg bw/d)	N/A	100 ppm: ↑bromodeoxyuridine (BrdU) labelling index in ♀ sacrificed day 7 500 ppm: ↑BrdU labelling index in ♂ sacrificed days 13, 27 and 59 and ♀ sacrificed days 7 and 13 2500 ppm: ↑absolute and relative liver weights (♂/♀), speckled liver, hepatocellular glycogenesis/fatty change, hepatocellular necrosis, apoptosis and pigmentation at 59 days, ↑BrdU labelling index in ♂ and ♀ sacrificed days 3, 7, 13 and 59
Assessment of replicative DNA synthesis in a 28-d dietary toxicity study	Rat, Tif:RAIf (SPF), 5 ♂ per dose at 0, 100, 1000, 2500 or 10000 ppm (Equal to 0, 8.0, 82, 199 or 711 mg/kg bw/d)	N/A	Immunohistochemical staining of liver sections from control and high-dose animals for proliferating cell nuclear antigen gave no indication for a treatment-related increase in the fraction of DNA-synthesizing hepatocytes in S-phase
Compound-induced mortality: No treatment-related mortality in short-term or chronic toxicity studies. Three unscheduled maternal deaths were observed at 150 mg/kg bw/d in the rabbit teratology study, and all 8 animals died at 500 mg/kg bw/d in the range finding rabbit teratology study.			
Recommended ARfD: The ARfD is 0.1 mg/kg bw, based on the NOAEL of 100 mg/kg bw established in the acute neurotoxicity study, with a 1000-fold uncertainty factor.			
Recommended ADI: The ADI is 0.0006 mg/kg bw/d, based on the NOAEL of 0.6 mg/kg bw/d established in the 2-generation rat reproduction study, with a 1000-fold uncertainty factor.			

Table 2 Endocrine-related findings observed in thiamethoxam toxicology database

Study	End point	Effect Level	No Effect Level
		(mg/kg bw/d)	
28-d gavage: rat	↑incidence of adrenocortical fatty change	300	100
28-d dietary: rat	hypertrophy of thyroid follicular epithelium: ♂ hypertrophy of thyroid follicular epithelium: ♀ fatty change of adrenal cortex and ↑cholesterol	199 763 711/763	82 211 199/211
90-d dietary: rat	↑cholesterol: ♂ adrenal fatty change: ♀ ↑absolute and relative adrenal weight: ♂	85182329	1893168
90-d dietary: mouse	↓absolute and relative ovary weight ovarian atrophy	626	231
28-d dermal: rat	inflammatory cell infiltration in adrenal cortex	250	60
28-d dietary: dog	↑thyroid weight: ♂ and ↓brain weight: ♀	48	32
90-d dietary: dog	↓testis and ovary weight associated with histopathological evidence of delayed maturation in ovaries and reduced spermatogenesis with minimal to moderate occurrence of spermatic giant cells in testes (at a dose that resulted in significant body weight loss, necessitating cessation of treatment for 7 days and resumption at a lower dose)	55/51	32/34
12-month dietary: dog	atrophy of seminiferous tubules	21	4.1
78-week dietary: mouse oncogenicity	↑absolute adrenal weight: ♀, interim sacrifice only, not statistically significant	479	215
2-generation reproduction: rat	↓testis weight (F_1) ↑incidence and severity of atrophy of seminiferous tubules (F_1) equivocal results on sperm motility in F_0 and F_1 (decreased at all doses tested, with no apparent dose-relationship), evaluated further in a separate, complementary study (F_0 only) that revealed no effect of treatment on sperm motility	158 1.8 N/A	61 0.6 N/A
Range finding developmental: rabbit	↓mean gravid uterus weight	150	50
Developmental: rabbit	hemorrhagic uterine contents, hemorrhagic discharge in the perineal area, ↑postimplantation loss	150	50

Appendix III Residues

Plant metabolism
The metabolism of thiamethoxam in pears, cucumbers, corn and rotational crops is similar, although the relative levels of individual metabolites differed among the three primary crops. Due to the quantitative differences observed in the cucumber metabolism study, FREAS cannot conclude that the metabolism of thiamethoxam in plants is understood. FREAS considers the corn metabolism study to be the most relevant to the petitioned use of a seed treatment on canola. To varying degrees, the metabolism of thiamethoxam in each of these crops involves: (*i*) opening of the oxadiazine ring by hydrolysis, (*ii*) loss of the nitro group, (*iii*) hydrolysis of the guanidine moiety to urea derivatives, (*iv*) cleavage of the N–C bridge between the two ring systems and (*v*) *N*-demethylation of the oxadiazine ring or its derivatives.

ROC: parent and metabolite CGA 322704 namely 3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-*N*-nitro-4*H*-1,3,5-oxadiazin-4-imine and the metabolite 1-(2-chloro-triazol-5-ylmethyl)-3-methyl-*N*-nitro-guanidine

Matrix	PHI (days)	^{14}C-thiazole TRR (ppm)	^{14}C-oxadiazine TRR (ppm)
pear (fruit)	15	6.806	7.071
cucumber (fruit) soil+foliar	14	0.295	0.323
corn (grain) soil drench	152–166	0.08	0.041

Confined crop rotation studies
0.2 kg a.i./ha (0.8× gap): Soil application

^{14}C-thiamethoxam equivalent residues (ppm)

Crop and fraction		Plant-back (d)					
		Thiazole label			Oxadiazine		
		29	119	362	29	119	362
Wheat	Forage	0.112	0	0.014	0.067	0.056	0.023
	Straw	0.753	0.17	0.051	0.52	0.233	0.057
	Grain	0.029	0.15	0.005	0.02	0.085	0.006
Radish	Foliage	0.116	0	0.009	0.077	0.011	0.008
	Roots	0.007	0	0.003	0.005	0.002	0.002
Leaf lettuce	Foliage	0.035	0	0.004	0.034	0.012	0.008
Soil (0–10 cm)		0.143	0.1	0.041	0.147	0.079	0.05

Freezer storage stability tests
Stability of thiamethoxam and CGA 322704 at –20°C in various matrices is illustrated below.
Plant metabolism and residue samples were stored within the time periods studied.

Crop matrix (fortification level)	Storage period (months)	Thiamethoxam		CGA 322704	
		Fresh recovery	% Recovered	Fresh recovery	% Recovered
Canola seed	6	65, 75	70, 85, 85	69, 73	72, 75, 78
	12	68, 84	74, 78, 78	94, 106	97, 100, 106
	24	84, 91	100, 100, 104	none	none
Canola oil	2	95, 96	97, 98	98, 99	49, 100
	4	95, 96	97, 99	98, 98	97, 98

Animal metabolism
The metabolism of thiamethoxam in rats, ruminants and poultry is similar. Excretion was rapid and occurred mostly through urine, but also in faeces. The major pathway of metabolism involves hydrolysis of the oxadiazine ring to form CGA 322704 and subsequent demethylation to produce CGA 265307; loss of the nitro group from these two metabolites also yields NOA 421275 and NOA 421276. Several major metabolites (MU3, L14 and MU12) in both ruminants and poultry also result from the reduction of the nitro group in thiamethoxam or CGA 265307 to a hydrazine, and subsequent conjugation with acetic or 2-oxo-propionic acids. Separation of the thiazole and oxadiazine rings was only a minor pathway in ruminants and poultry.

ROC: parent and metabolite CGA 322704 namely 3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-*N*-nitro-4*H*-1,3,5-oxadiazin-4-imine and the metabolite 1-(2-chloro-triazol-5-ylmethyl)-3-methyl-*N*-nitro-guanidine

Matrix	% administered dose (ppm)
Goat tissues	3.4–3.7% (20.6–22.7)
Milk	<1% (1.9–2.3)
Faeces	8–12%
Urine	44–49%

Cattle feeding study
Using the proposed U.S. tolerances (from the petitioned use pattern), daily intake of thiamethoxam for beef cattle is 0.93 ppm, based on a diet consisting of 40% apple pomace, 20% cotton gin by-products, 25% wheat forage and 15% barley or wheat grain, and 1.43 ppm for dairy cattle, based on a diet consisting of 60% wheat forage, 20% cotton gin by-products and 20% barley or wheat grain. The expected residues in canola meal are 0.0015 ppm, and based on a ~2.0 ppm feeding level, the PMRA can conclude that there are no finite residues transferred in the meat and milk.

The available data support the proposed MRL (at the LOQs) for milk (0.01 ppm), and for meat and meat by-products (0.02 ppm).

Hen feeding study
The maximum theoretical dietary burden of thiamethoxam for swine and poultry is 0.025 ppm, based on a diet consisting of 85% sorghum grain and 15% cottonseed meal for swine, and 80% wheat or sorghum grain and 20% cottonseed meal for poultry. As the 2 ppm feeding level in the current study represents 80× the theoretical dietary burden for swine, there is no reasonable expectation of the transfer of thiamethoxam residues from feed items to hog commodities. In the poultry metabolism study, hens were dosed at ~100 ppm, equivalent to ~4000× the maximum dietary burden. Based on data from the metabolism study, residues of thiamethoxam and CGA 322704 in tissues and eggs would be expected to be <0.01 ppm even at a 100× feeding level.

The available data support the proposed MRL (at the LOQs) for poultry meat and eggs (0.02 ppm).

Number of field trials by region*

For canola

Zones	1	5	5B	7	0.292	9	11	12	14	Total
Required		1		1					14	16
Submitted		4		2	1				13	20

*Trials were carried out over a total of 3 growing seasons. Eight additional trials from the U.S. were also submitted.

For mustard seed										
Zones	1	5	5B	7	0.292	9	11	12	14	Total
Required				2					3	5
Submitted				1	1				3	5

Supervised residue trials						
Commodity and portion analysed	**Formulation**	**Application**			**PHI (days)**	**Residues (ppm)****
		No.	**Total rate (kg a.i./100 kg seed)**	**% gap**		
Canadian + U.S. trials on canola						
Canola seed	Seed	1	0.4	1	87–295	<0.02
Canadian trials on mustard						
Mustard seed	Seed treatment	1	0.4	1×	101–104	<0.02

Processing studies
Residue trials were carried out at 3× the proposed label rate. No detectable residues were observed in the harvested seed. As the 3× rate is equal to the maximum theoretical concentration factor, the PMRA will conclude that residues of thiamethoxam and CGA 322704 do not concentrate in canola oil.

Chronic dietary risk assessment using DEEM Software based on the 1994–1996 Continuing Survey of Food Intake by Individuals: Q* 3.771 × 10^{-2}: using the proposed MRLs for canola and mustard only, no allocation to water due to no mobility, and no contribution from meat, milk and eggs, as no finite residues likely

	All U.S. populations	**All infants (<1 year)**	**Children (1–6 years)**	**Children (7–12 years)**	**Children (13–19 years)**	**20+ years**	**Seniors (55+ years)**
Life-time risk	5.4×10^{-9}	2.8×10^{-10}	8.5×10^{-9}	6.4×10^{-9}	5.3×10^{-9}	4.9×10^{-9}	4.5×10^{-9}

Proposed MRLs		
Commodity	**Proposed Canadian MRLs (ppm)**	**U.S. tolerances (ppm)**
canola seed, mustard seed	0.02	Unknown
eggs, meat and meat by-products	0.02	
milk	0.01	

Appendix IV Environmental assessment

Table 1 Summary of terrestrial fate and transformation data

Fate process	End point	Interpretation
Hydrolysis	$t_{½}$ pH 5: not determined $t_{½}$ pH 7: 643d $t_{½}$ pH 9: 8.4 d	Hydrolysis will not be a route for transformation or dissipation of thiamethoxam in acidic to neutral environmental media, but will be important in an alkaline environment.
Phototransformation	not determined	—
Aerobic biotransformation	$t_{½}$: 294, 336 and 353 d	Thiamethoxam is classed as moderately persistent to persistent in soil under aerobic conditions.
Anaerobic biotransformation	no data were submitted	—
Adsorption and desorption	Adsorption K_{oc}: 33.1–176.7 mL/g carbon Desorption K_{oc}: 72.1–697.5 mL/g carbon	Thiamethoxam has a medium to very high potential for mobility in the soil. Once adsorbed to soil, thiamethoxam would be less likely to be mobile in the soil.
Aged soil column leaching	low mobility	Thiamethoxam will be less mobile in soil after ageing.
Field dissipation and leaching	DT_{50}: 72–111 d No residues of parent compound and transformation products below the 25 cm soil depth	Thiamethoxam is moderately persistent in soil under field conditions. Thiamethoxam did not leach appreciably under conditions of the seed treatment field study.

Table 2 Summary of transformation products formed in terrestrial fate studies

Fate process	Major transformation products (% of applied thiamethoxam)	Minor transformation products (% of applied thiamethoxam)
Hydrolysis	CGA 355190 and NOA 404617 (59.4 and 27.8%, respectively) from ^{14}C-guanidine-thiamethoxam and CGA 355190, CGA 404617 and CGA 309995 from ^{14}C-thiazolyl-thiamethoxam (54.3, 35.2 and 9.1%, respectively)	None
Phototransformation on soil	—	—
Aerobic biotransformation	CGA 355190 (23% by month 6), further transformed to CGA 353968	30 minor transformation products detected by 2-D TLC
Aged soil column leaching	None	Several minor transformation products detected in leachates and soil segments
Terrestrial field dissipation	CGA 355190 and CGA 322704	None

Table 3 Summary of toxicity of thiamethoxam to terrestrial organisms

Group	Organism	Study	NOEL or NOEC	LD_{50}, LC_{50} or EC_{25}	Interpretation
Birds	bobwhite quail	acute oral	125 mg a.i./kg bw	1552 mg a.i./kg bw	slightly toxic
	bobwhite quail	dietary	1300 mg a.i./kg diet	>5200 mg a.i./kg diet	practically nontoxic
	mallard duck	acute oral	not determined	576 mg a.i./kg bw	slightly toxic
	mallard duck	dietary	163 mg a.i./kg diet	>5200 mg a.i./kg diet	practically nontoxic
	bobwhite quail	reproduction	900 mg a.i./kg diet	—	no significant treatment-related effects
	mallard duck	reproduction	300 mg a.i./kg diet	—	no significant treatment-related effects

Table 4 Summary of risk assessment for terrestrial organisms

Organism	Effect	NOEC or NOEL	EEC	Margin of safety	Risk	Mitigatory measures
Bobwhite quail	dietary	1300 mg a.i./kg diet	151.7 mg a.i./kg bw/d	8.57	no risk	none
Mallard duck	dietary	163 mg a.i./kg diet	88.9 mg a.i./kg bw/d	1.83	no risk	none